

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 July 2001 (12.07.2001)

PCT

(10) International Publication Number
WO 01/49289 A1

(51) International Patent Classification⁷: **A61K 31/42**,
A61P 9/00, 15/06, 15/12, 43/00

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(21) International Application Number: PCT/US00/35280

(22) International Filing Date:
27 December 2000 (27.12.2000)

(81) Designated States (*national*): AE, AG, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/174,125 31 December 1999 (31.12.1999) US

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier application:
US 60/174,125 (CIP)
Filed on 31 December 1999 (31.12.1999)

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Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

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*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: PHARMACEUTICAL AND VETERINARY USES OF ENDOTHELIN ANTAGONISTS

(57) Abstract: Pharmaceutical and veterinary uses of endothelin antagonists are provided. In particular, methods of treatment of laminitis, such as equine and bovine laminitis, by administration of one or more endothelin antagonists are provided. Methods of treatment, prevention, or amelioration of one or more symptoms of menopause; osteoporosis and metabolic bone disorders; climacteric disorders including hot flushes or flashes, abnormal clotting patterns, urogenital discomfort and increased incidence of cardiovascular disease, and other disorders associated with the reduction in ovarian function in women; pre-eclampsia; and control and management of labor during pregnancy by administration of endothelin antagonists are also provided.

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PHARMACEUTICAL AND VETERINARY USES OF ENDOTHELIN ANTAGONISTS

RELATED APPLICATIONS

For International purposes benefit of priority is claimed to U.S. provisional application No. 60/174,125, filed December 31, 1999, to Thomas A. Brock and Patrick R. Ward, entitled "PHARMACEUTICAL AND VETERINARY USES OF ENDOTHELIN ANTAGONISTS". For U.S. purposes benefit of priority under 35 U.S.C. §119(e) is claimed to U.S. provisional application No. 60/174,125. For U.S. purposes and where permitted, the above-referenced application is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

Provided herein are pharmaceutical and veterinary uses of endothelin antagonists. In particular, methods of treatment, prevention, or amelioration of one or more symptoms of equine or bovine laminitis by administration of endothelin antagonists are provided. Methods of treatment, prevention, or amelioration of one or more symptoms of menopause; osteoporosis and metabolic bone disorders; climacteric disorders including hot flushes or flashes, abnormal clotting patterns, urogenital discomfort and increased incidence of cardiovascular disease, and other disorders associated with the reduction in ovarian function in middle-aged women; pre-eclampsia; and control and management of labor during pregnancy by administration of endothelin antagonists are also provided.

BACKGROUND OF THE INVENTION

Endothelin

The vascular endothelium releases a variety of vasoactive substances, including the endothelium-derived vasoconstrictor peptide, endothelin (ET) (see, e.g., Vanhoutte *et al.* (1986) *Annual Rev. Physiol.* 48: 307-320; Furchgott and Zawadski (1980) *Nature* 288: 373-376). Endothelin, which was originally identified in the culture supernatant of porcine aortic endothelial cells (see, Yanagisawa *et al.* (1988) *Nature* 332: 411-415), is a potent twenty-one amino acid peptide vasoconstrictor. It is the most potent vasopressor known and is produced by numerous cell types, including the cells of the endothelium, trachea, kidney and brain. Endothelin is synthesized as a two hundred and three amino acid precursor preproendothelin that contains a signal sequence which is cleaved by an endogenous protease to produce a thirty-eight (human) or thirty-nine (porcine) amino acid peptide. This intermediate, referred to as big endothelin, is processed *in vivo* to the mature biologically active form by a putative endothelin-

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converting enzyme (ECE) that appears to be a metal-dependent neutral protease (see, e.g., Kashiwabara *et al.* (1989) *FEBS Ltrrs.* 247: 337-340). Cleavage is required for induction of physiological responses (see, e.g., von Geldern *et al.* (1991) *Peptide Res.* 4: 32-35). In porcine aortic endothelial cells, the thirty-nine amino acid intermediate, big endothelin, is hydrolyzed at the Trp²¹-Val²² bond to generate endothelin-1 and a C-terminal fragment. A similar cleavage occurs in human cells from a thirty-eight amino acid intermediate. Three distinct endothelin isopeptides, endothelin-1, endothelin-2 and endothelin-3, that exhibit potent vasoconstrictor activity have been identified.

The family of three isopeptides endothelin-1, endothelin-2 and endothelin-3 are encoded by a family of three genes (see, Inoue *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86: 2863-2867; see, also Saida *et al.* (1989) *J. Biol. Chem.* 264: 14613-14616). The nucleotide sequences of the three human genes are highly conserved within the region encoding the mature 21 amino acid peptides and the C-terminal portions of the peptides are identical. Endothelin-2 is (Trp⁶,Leu⁷) endothelin-1 and endothelin-3 is (Thr²,Phe⁴,Thr⁵,Tyr⁶,Lys⁷,Tyr¹⁴) endothelin-1. These peptides are, thus, highly conserved at the C-terminal ends. Release of endothelins from cultured endothelial cells is modulated by a variety of chemical and physical stimuli and appears to be regulated at the level of transcription and/or translation. Expression of the gene encoding endothelin-1 is increased by chemical stimuli, including adrenaline, thrombin and Ca²⁺ ionophore. Endothelial cells appear to secrete short-lived endothelium-derived relaxing factors (EDRF), now known to be nitric oxide, when stimulated by vasoactive agents, such as acetylcholine and bradykinin. Endothelin-induced vasoconstriction is also attenuated by atrial natriuretic peptide (ANP).

Laminitis

Equine laminitis, which is sometimes referred to as foundering, is a common disorder that was recognized and described in the earliest books of veterinary medicine. Laminitis is an inflammation of the pedal laminae that form the supportive bond between the hoof and the third phalanx (see, Green, M. E., *et al.* (1991) *Equine Medicine and Surgery*, Fourth Edition, Vol. II, Colahan, P. T. *et al.* (Eds.), American Veterinary Publications, Inc., Chapter 12, pp. 1354-1358). Laminitis is further described as a disorder of the hoof whose cause is varied. It is a complex, multi-systemic disease affecting the digestive, cardiovascular, hemic, renal, endocrine, musculoskeletal, integumentary, and immune systems. It is characterized by multi-systemic aberrations that ultimately result in reduced capillary perfusion, ischemia, and necrosis of the

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laminae. These results are accompanied by pain and loss of supportive function. See, generally, equine laminitis: Katwa *et al.* (1999) Equine Vet. J. **31**(3):243-247; MacEachern *et al.* (1997) Res. Vet. Sci. **62**(2):147-152; Benamou *et al.* (1998) Pulm. PHarm. Ther. **11**:231-235; bovine laminitis: Corder *et al.* (1999) J. Cardiovasc. Pharmacol. **33**(4):671-677; Desmarests *et al.* (1999) Biochem. Biophys. Res. Commun. **256**(2):357-360; Acosta *et al.* (1998) Biol. Reprod. **59**(2):437-443.

Acute laminitis is described as comprising the events leading up to and the onset of lameness. Acute laminitis can progress to the chronic stage. The chronic stage ensues after persistent lameness (greater than 48 hours), or when the distal phalanx deviates detectably. Chronic laminitis is a consequence of some degree of loss of integrity of the supporting digital laminae. In the chronic phase, the horse assumes a recumbent position in which most of the weight is placed on the hind limbs and little weight bearing pressure is exerted on the forelimbs.

There are reports of evidence that equine laminitis is caused by ingestion of too much grain; colic; retained placenta; exhaustion; ingestion of black walnut shavings; ingestion of too rich grass; excessive concussion, and/or excessive cold water. Despite the gathering of voluminous information over a period exceeding 300 years, equine laminitis still remains incompletely understood and appears to be multifactorial (see, *e.g.*, Hinckley, *et al.* (1994) J. Endocrinol. **143**:P103, which illustrates the complexity of the aetiology of laminitis.

While it is possible that an equine with this condition can recover without intervention treatment, during the course of the disease there is substantial pain, recumbency, hoof wall deformation and even sloughing of the hooves. Several symptoms are displayed, including: a bounding digital pulse, warm feet, an abnormal gait, a shifting of weight, or some combination of some or all of these. If the animal does not recover, after the onset of lameness, the laminae deteriorate, the animal's feet are extremely painful, and the coffin bone becomes displaced.

Current therapies for equine laminitis include treatment with nitroglycerin, applied transdermally, and isoxsuprine, administered orally; and/or an anticoagulant, such as heparin, aspirin and trental (pentoxifylline) and others (see, U.S. Patent No. 5,891,472; see also, Elliott, J. (1996) Equine Vet. J. **28**(1):1-2). All current therapies suffer from one or more drawbacks, including difficulty in the mode of administration of the active drug, lack of effectiveness, lack of compliance and lack of simplicity in the proposed treatment regimen.

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Another treatment for equine laminitis involves use of intravenously administered L-Arg and topically applied nitroglycerin (glyceryl trinitrate or GTN) (see, Hinckley et al., (1996) Equine Vet. J. 28(1):17-28). The L-Arg is administered i.v. as a 10% aqueous solution, while the GTN is provided as a 2% ointment through a patch that is

5 positioned, using adhesive tape, over digital vessels. In particular, a laminitic pony, weighing 250 kg, received a total dose of 120 g of L-Arg or 0.48 g/kg bwt at a rate of approximately 40 mL/min (16 mg/kg bwt/min) for 30 min. The GTN patches were also applied once daily to three limbs only, 12 hours after the L-Arg infusion. Drops in heart rates were observed, including hypotension and cardiac arrhythmia, with the i.v.

10 infusion. Some ponies showed signs of pain, sweating and shivering. The topical application of GTN patches appeared to improve the lameness of some of the treated ponies. No improvement was observed in others. Thus, it is clear that L-Arg, given intravenously, is not a particularly effective treatment.

Thus, there is a need for an effective treatment of laminitis, particularly equine

15 or bovine laminitis. Therefore, it is an object herein to provide methods of treating, preventing, or ameliorating one or more symptoms of laminitis, particularly equine or bovine laminitis, more particularly equine laminitis.

SUMMARY OF THE INVENTION

Pharmaceutical and veterinary uses of compounds that modulate the interaction

20 of an endothelin peptide with an endothelin receptor are provided. In certain embodiments, veterinary uses of endothelin antagonists are provided herein. In particular, methods of treatment, prevention, or amelioration of one or more symptoms of laminitis, which afflict animals with hooves, particularly equine or bovine laminitis, using endothelin antagonists are provided. In other embodiments, pharmaceutical uses

25 of endothelin antagonists are provided.

The pharmaceutical and veterinary methods provided herein use any compound capable of inhibiting the activity of endothelin peptides; or use any compound that is an endothelin receptor antagonist. In particular, methods of using endothelin antagonists, particularly sulfonamide compounds, for the treatment of disorders involving nitric

30 oxide, such as equine laminitis, are provided. Any compound, particularly any sulfonamide, known to those of skill in the art to have endothelin antagonist activity, particularly ET_A antagonist activity, is contemplated for use herein. Numerous such endothelin antagonists are known to those of skill in the art (see, e.g., U.S. Patent Nos. 6,133,442, 6,133,263, 6,107,320, 6,083,955; 6,083,951; 6,080,774; 6,063,911;

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5,753,619; 5,739,333; 5,736,564; 5,731,434; 5,731,321; 5,728,706; 5,726,194;
5,719,183; 5,719,182; 5,716,985; 5,716,984; 5,714,479; 5,703,106; 5,700,807;
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- Also of interest are any pharmaceutically or veterinarily acceptable derivatives, including salts, esters, acids and bases, solvates, hydrates and prodrugs of the compounds. Preferred are pharmaceutically or veterinarily acceptable salts, including, but not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine, tris(hydroxymethyl)aminomethane, alkali metal salts, such as but not limited to lithium, potassium and sodium, alkali earth metal salts, such as but not limited to barium, calcium and magnesium, transition metal salts, such as but not limited to, zinc and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate, preferably sodium salts, more preferably the sodium salt, and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates, salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and

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fumarates. Alkali metal salts, particularly sodium salts, are preferred herein. Most preferred salts are sodium salts.

Pharmaceutical and veterinary formulations for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein or pharmaceutically or veterinarily acceptable derivatives thereof, preferably salts, more preferably sodium salts, including but not limited to sodium salts and sodium hydrogen phosphate salts, most preferably the sodium salt, thereof that deliver amounts effective for the treatment, prevention, or amelioration of one or more symptoms of laminitis, particularly equine or bovine laminitis; menopause; osteoporosis and metabolic bone disorders; climacteric disorders including hot flushes or flashes, abnormal clotting patterns, urogenital discomfort and increased incidence of cardiovascular disease; and other disorders associated with the reduction in ovarian function in middle-aged women; pre-eclampsia; and control and management of labor during pregnancy by administration of endothelin antagonists are also provided. The formulations are compositions suitable for administration by any desired abnormal clotting patterns, urogenital discomfort and increased incidence of route and include solutions, suspensions, emulsions, tablets, dispersible tablets, pills, cardiovascular disease, and other disorders associated with the reduction in ovarian capsules, powders, dry powders for inhalation, sustained release formulations, aerosols function in middle-aged women; pre-eclampsia; and control and management of labor for nasal and respiratory delivery, patches for transdermal delivery and any other during pregnancy are also provided. suitable route. The compositions should be suitable for oral administration, parenteral administration by injection, including subcutaneously, intramuscularly or intravenously as an injectable aqueous or oily solution or emulsion, transdermal administration and other selected routes.

Methods for treatment, prevention, or amelioration of one or more symptoms of endothelin-mediated disorders, including, but not limited to, laminitis, particularly equine or bovine laminitis, more particularly equine laminitis; menopause; osteoporosis and metabolic bone disorders; climacteric disorders including hot flushes or flashes, abnormal clotting patterns, urogenital discomfort and increased incidence of cardiovascular disease associated with menopause, and other disorders associated with the reduction in ovarian function in middle-aged and older women; pre-eclampsia; and control and management of labor during pregnancy are provided.

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In particular, methods of treating laminitis by administering effective amounts of the compounds, or veterinarily acceptable derivatives thereof, are provided. In particular, methods for treating laminitis, particularly equine or bovine laminitis, more particularly equine laminitis, by administering effective amounts of one or more of the
5 compounds provided herein in veterinarily acceptable carriers are provided. Preferred methods of treatment are methods for treatment of equine laminitis.

Also provided are methods of treatment, prevention, or amelioration of one or more symptoms of menopause; osteoporosis and metabolic bone disorders; climacteric disorders including hot flushes or flashes, abnormal clotting patterns, urogenital
10 discomfort and increased incidence of cardiovascular disease, and other disorders associated with the reduction in ovarian function in middle-aged and older women; pre-eclampsia; and control and management of labor during pregnancy.

Of the methods of treatment, more preferred are those in which the formulations contain at least one compound that inhibits the interaction of endothelin-1 with ET_A
15 receptors at an IC_{50} of less than about $10 \mu M$, and preferably less than about $5 \mu M$, more preferably less than about $1 \mu M$, even more preferably less than $0.1 \mu M$, and most preferably less than $0.05 \mu M$. Other preferred methods are those in which the formulations contain pharmaceutically or veterinarily acceptable derivatives, preferably salts, of one or more compounds that is (are) ET_A selective, or pharmaceutically or
20 veterinarily acceptable derivatives, preferably salts, of one or more compounds that is (are) ET_B selective.

In practicing the methods, effective amounts of formulations containing therapeutically effective concentrations of the compounds formulated for oral, intravenous, local and topical application for the treatment of laminitis, particularly
25 equine or bovine laminitis, more particularly equine laminitis; menopause; osteoporosis and metabolic bone disorders; climacteric disorders including hot flushes or flashes, abnormal clotting patterns, urogenital discomfort and increased incidence of cardiovascular disease, and other disorders associated with the reduction in ovarian function in middle-aged women; pre-eclampsia; and control and management of labor
30 during pregnancy are provided are administered to an individual exhibiting the symptoms of one or more of these disorders. The amounts are effective to ameliorate or eliminate one or more symptoms of the disorders.

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DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS**Definitions**

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this

5 invention belongs. Where permitted, all patents, published patent applications, patent applications and publications referred to throughout the disclosure are incorporated by reference.

As used herein, "laminitis" or "foundering" refers to an inflammation of the pedal laminae that form the supportive bond between the hoof and the third phalanx.

10 Laminitis is characterized by multi-systemic aberrations that ultimately result in reduced capillary perfusion, ischemia, and necrosis of the laminae, accompanied by pain, loss of supportive function, and ultimately lameness.

As used herein, endothelin (ET) peptides include peptides that have substantially the amino acid sequence of endothelin-1, endothelin-2 or endothelin-3 and that act as
15 potent endogenous vasoconstrictor peptides.

As used herein, an endothelin-mediated condition is a condition that is caused by abnormal endothelin activity or one in which compounds that inhibit endothelin activity have therapeutic use. Such diseases include, but are not limited to hypertension, cardiovascular disease, asthma, inflammatory diseases, ophthalmologic
20 disease, menstrual disorders, obstetric conditions, gastroenteric disease, renal failure, pulmonary hypertension, endotoxin shock, anaphylactic shock, hemorrhagic shock, climacteric disorders, menopause, hot flushes or flashes, osteoporosis, preterm labor, pre-eclampsia, eclampsia and metabolic bone disorders. Endothelin-mediated conditions also include conditions that result from therapy with agents, such as erythropoietin and
25 immunosuppressants, that elevate endothelin levels.

As used herein an effective amount of a compound for treating a particular disease is an amount that is sufficient to ameliorate, or in some manner reduce the symptoms associated with the disease. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective. The
30 amount may cure the disease but, typically, is administered in order to ameliorate the symptoms of the disease. Typically, repeated administration is required to achieve the desired amelioration of symptoms.

As used herein, an endothelin agonist is a compound that potentiates or exhibits a biological activity associated with or possessed by an endothelin peptide.

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- As used herein, an endothelin antagonist is a compound, such as a drug or an antibody, that inhibits endothelin-stimulated vasoconstriction and contraction and other endothelin-mediated physiological responses. The antagonist may act by interfering with the interaction of the endothelin with an endothelin-specific receptor or by
- 5 interfering with the physiological response to or bioactivity of an endothelin isopeptide, such as vasoconstriction. Thus, as used herein, an endothelin antagonist interferes with endothelin-stimulated vasoconstriction or other response or interferes with the interaction of an endothelin with an endothelin-specific receptor, such as ET_A receptors, as assessed by assays known to those of skill in the art.
- 10 The effectiveness of potential agonists and antagonists can be assessed using methods known to those of skill in the art. For example, endothelin agonist activity can be identified by its ability to stimulate vasoconstriction of isolated rat thoracic aorta or portal vein ring segments (Borges et al. (1989) "Tissue selectivity of endothelin" Eur. J. Pharmacol. 165: 223-230). Endothelin antagonist activity can be assessed by the
- 15 ability to interfere with endothelin-induced vasoconstriction. Exemplary assays are set forth in the EXAMPLES. As noted above, the preferred IC₅₀ concentration ranges are set forth with reference to assays in which the test compound is incubated with the ET receptor-bearing cells at 4° C. Data presented for assays in which the incubation step is performed at the less preferred 24° C are identified. It is understood that for purposes
- 20 of comparison, these concentrations are somewhat higher than the concentrations determined at 4° C.

- As used herein, the biological activity or bioactivity of endothelin includes any activity induced, potentiated or influenced by endothelin in vivo. It also includes the ability to bind to particular receptors and to induce a functional response, such as
- 25 vasoconstriction. It may be assessed by in vivo assays or by in vitro assays, such as those exemplified herein. The relevant activities include, but are not limited to, vasoconstriction, vasorelaxation and bronchodilation. For example, ET_B receptors appear to be expressed in vascular endothelial cells and may mediate vasodilation and other such responses; whereas ET_A receptors, which are endothelin-1-specific, occur on
- 30 smooth muscle and are linked to vasoconstriction. Any assay known to those of skill in the art to measure or detect such activity may be used to assess such activity (see, e.g., Spokes et al. (1989) J. Cardiovasc. Pharmacol. 13(Suppl. 5):S191-S192; Spinella et al. (1991) Proc. Natl. Acad. Sci. USA 88: 7443-7446; Cardell et al. (1991) Neurochem. Int. 18:571-574); and the Examples herein).

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As used herein, bioavailability refers to the rate and extent of absorption. Methods for determining bioavailability are well known to those of skill in the art. For example, bioavailability of any of the compounds described herein can be determined empirically by administration of the compound to an animal, followed by taking blood

5 samples over time and measuring the blood concentration of the compound. In vivo half life ($t_{1/2}$) is defined as the time it takes for the concentration of the compound in the blood to be reduced by one-half. Estimations of the area under the curve for intravenous administration can be used to estimate the area under the curve for oral administration, yielding bioavailability data. See, e.g., Milo Gibal (1991)

10 Biopharmaceutics and Pharmacology, 4th edition (Lea and Sediger).

As used herein, efficacy refers to the maximal effect that can be produced by a compound. Efficacy can be determined by methods known to those of skill in the art. For example, it can be determined by the properties of the compound and its receptor-effector system and is reflected in the plateau of the concentration-effect curve. In vivo

15 efficacy refers to efficacy which is determined in an animal model. For example, in vivo efficacy of the compounds described herein can be determined by amelioration of hypoxia-induced pulmonary hypertension in rat. In this context, in vivo efficacy refers to the ability of a compound to restore an elevated pulmonary artery pressure to a normal value. See, e.g., DiCarlo et al. (1995) Am. J. Physiol. 269:L690-L697.

20 As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as binding of endothelin to tissue receptors, in an assay that measures such response.

As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of

25 a particular response that is induced, provoked or potentiated by the particular test compound.

As used herein a sulfonamide that is ET_A selective refers to sulfonamides that exhibit an IC_{50} that is at least about 10-fold lower with respect to ET_A receptors than ET_B receptors.

30 As used herein, a sulfonamide that is ET_B selective refers to sulfonamides that exhibit an IC_{50} that is at least about 10-fold lower with respect to ET_B receptors than ET_A receptors.

As used herein, pharmaceutically or veterinarily-acceptable salts, esters, hydrates, solvates or other derivatives of the compounds include any such salts, esters

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and other derivatives that may be prepared by those of skill in this art using known methods for such derivatization and that produce compounds that may be administered to animals or humans without substantial toxic effects and that either are pharmaceutically or veterinarily active or are prodrugs. Pharmaceutically and

5 veterinarily-acceptable salts include, but are not limited to, salts of alkali metals and alkaline earth metals, including but not limited to sodium salts, potassium salts, lithium salts, calcium salts and magnesium salts; transition metal salts, such as zinc salts, copper salts and aluminum salts; polycationic counter ion salts, such as but not limited ammonium and substituted ammonium salts and organic amine salts, such as

10 hydroxyalkylamines and alkylamines; salts of mineral acids, such as but not limited to hydrochlorides and sulfates, salts of organic acids, such as but not limited acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrate, valerate and fumarates. Also contemplated herein are the corresponding esters.

Preferred pharmaceutically or veterinarily-acceptable salts include, but are not

15 limited to, N,N'-dibenzylethylenediamine, chlorprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine, tris(hydroxymethyl)aminomethane, aluminum, calcium, lithium, magnesium, potassium,

20 sodium hydrogen phosphate, disodium phosphate, sodium, zinc, barium, gold, silver and bismuth salts. Sodium salts, particularly the sodium salt of each of the compound, are most preferred herein.

As used herein, reference to "sodium salts" refers to salts of any sodium compounds in which the counter ion includes Na^+ and can include other ions, such as

25 HPO_4^{2-} ; reference to a "sodium salt" (rather than sodium salts) refers specifically to a salt in which Na^+ is the counter ion.

As used herein, treatment means any manner in which the symptoms of a conditions, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical or veterinary use of the compositions

30 herein, such as use as contraceptive agents.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical or veterinary composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

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- As used herein, nitric oxide "donors" or "precursors" refer to compounds such as sodium nitroprusside, nitroglycerin, sodium nitrite, hydroxylamine, sodium azide and other nitrogen-containing compounds that function as smooth muscle relaxing agents. The activity of a variety of smooth muscle relaxing agents, including sodium
- 5 nitroprusside, nitroglycerin and sodium nitrite, may be related to their ability to increase tissue levels of cyclic guanosine monophosphate (cGMP) or to the formation of nitric oxide (NO) (see, Katsuki, et al. (1977) J. Cyclic Nucleotide Res. 3:25-35). Other nitrogen-containing compounds may also function similarly, including hydroxylamine or sodium azide, and also may possess vasodilatory properties.
- 10 As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis and high performance liquid chromatography (HPLC), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical
- 15 and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.
- 20 As used herein, biological activity refers to the in vivo activities of a compound or physiological responses that result upon in vivo administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmaceutical or veterinary activity of such compounds, compositions and mixtures.
- 25 As used herein, increased stability of a formulation means that the percent of active component present in the formulation, as determined by assays known to those of skill in the art, such as high performance liquid chromatography, gas chromatography, and the like, at a given period of time following preparation of the formulation is significantly higher than the percent of active component present in
- 30 another formulation at the same period of time following preparation of the formulation. In this case, the former formulation is said to possess increased stability relative to the latter formulation.

As used herein, a prodrug is a compound that, upon in vivo administration, is metabolized or otherwise converted to the biologically, pharmaceutically, veterinarily or

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therapeutically active form of the compound. To produce a prodrug, the pharmaceutically or veterinarily active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically or veterinarily active compound is known, can design prodrugs of the compound (see, e.g., Nogrady (1985) Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392). For example, succinyl-sulfathiazole is a prodrug of 4-amino-N-(2-thiazolyl)benzenesulfonamide (sulfathiazole) that exhibits altered transport characteristics.

As used herein, acid isostere means a group that is significantly ionized at physiological pH. Examples of suitable acid isosteres include sulfo, phosphono, alkylsulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl or heteroaryl sulfonylcarbamoyl.

As used herein, halo or halide refers to the halogen atoms; F, Cl, Br and I.

As used herein, pseudohalides are compounds that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides (X⁻, in which X is a halogen, such as Cl or Br). Pseudohalides include, but are not limited to cyanide, cyanate, thiocyanate, selenocyanate and azide.

As used herein, haloalkyl refers to a loweralkyl radical in which one or more of the hydrogen atoms are replaced by halogen including, but not limited to, chloromethyl, trifluoromethyl, 1-chloro-2-fluoroethyl and the like.

As used herein, alkyl means an aliphatic hydrocarbon group that is a straight or branched chain preferably having about 1 to 12 carbon atoms in the chain. Preferred alkyl groups are loweralkyl groups which are alkyls containing 1 to about 6 carbon atoms in the chain. Branched means that one or more loweralkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. The alkyl group may be unsubstituted or independently substituted by one or more groups, such as, but not limited to: halo, carboxy, formyl, sulfo, sulfinio, carbamoyl, amino and imino. Exemplary alkyl groups include methyl, ethyl, propyl, carboxymethyl, carboxyethyl, carboxypropyl, ethanesulfinic acid and ethane sulfonic acid.

As used herein the term lower describes alkyl, alkenyl and alkynyl groups containing about 6 carbon atoms or fewer. It is also used to describe aryl groups or

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heteroaryl groups that contain 6 or fewer atoms in the ring. Loweralkyl, lower alkenyl, and lower alkynyl refer to carbon chains having less than about 6 carbons. In preferred embodiments of the compounds provided herein that include alkyl, alkenyl, or alkynyl portions include loweralkyl, lower alkenyl, and lower alkynyl portions.

- 5 As used herein, alkenyl means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched chained having from about 2 to about 10 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 4 carbon atoms in the chain. Branched means that one or more loweralkyl or lower alkenyl groups are attached to a linear alkenyl chain. The alkenyl group may be
- 10 unsubstituted or independently substituted by one or more groups, such as halo, carboxy, formyl, sulfo, sulfinio, carbamoyl, amino and imino. Exemplary alkenyl groups include ethenyl, propenyl, carboxyethenyl, carboxypropenyl, sulfinoethenyl and sulfonoethenyl.

- As used herein, alkynyl means an aliphatic hydrocarbon group containing a
- 15 carbon-carbon triple bond and which may be straight or branched having about 2 to 10 carbon atoms in the chain. Branched means that one or more loweralkyl, alkenyl or alkynyl groups are attached to a linear alkynyl chain. An exemplary alkynyl group is ethynyl.

- As used herein, aryl means an aromatic monocyclic or multicyclic hydrocarbon
- 20 ring system containing from 3 to 15 or 16 carbon atoms, preferably from 5 to 10. Aryl groups include, but are not limited to groups, such as phenyl, substituted phenyl, naphthyl, substituted naphthyl, in which the substituent is loweralkyl, halogen, or lower alkoxy. Preferred aryl groups are lower aryl groups that contain less than 7 carbons in the ring structure.

- 25 As used herein, the nomenclature alkyl, alkoxy, carbonyl, etc. are used as is generally understood by those of skill in this art. For example, as used herein alkyl refers to saturated carbon chains that contain one or more carbons; the chains may be straight or branched or include cyclic portions or be cyclic. As used herein, alicyclic refers to aryl groups that are cyclic.

- 30 As used herein, cycloalkyl refers to saturated cyclic carbon chains; cycloalkenyl and cycloalkynyl refer to cyclic carbon chains that include at least one unsaturated double or triple bond, respectively. The cyclic portions of the carbon chains may include one ring or two or more fused rings.

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As used herein, cycloalkenyl means a non-aromatic monocyclic or multicyclic ring system containing a carbon-carbon double bond and having about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl or cyclohexenyl; preferred is cyclohexenyl. An exemplary multicyclic cycloalkenyl ring is norbornenyl. The cycloalkenyl group may be independently substituted by one or more halo or alkyl.

As used herein, "haloalkyl" refers to a loweralkyl radical in which one or more of the hydrogen atoms are replaced by halogen including, but not limited to, chloromethyl, trifluoromethyl, 1-chloro-2-fluoroethyl and the like.

10 As used herein, "haloalkoxy" refers to RO- in which R is a haloalkyl group.

As used herein, "carboxamide" refers to groups of formula $R_p\text{CONH}_2$ in which R is selected from alkyl or aryl, preferably loweralkyl or lower aryl and p is 0 or 1.

As used herein, "alkylaminocarbonyl" refers to -C(O)NHR in which R is hydrogen, alkyl, preferably loweralkyl or aryl, preferably lower aryl.

15 As used herein "dialkylaminocarbonyl" as used herein refers to -C(O)NR'R in which R' and R are independently selected from alkyl or aryl, preferably loweralkyl or loweraryl; "carboxamide" refers to groups of formula $\text{NR}'\text{COR}$.

As used herein, "alkoxycarbonyl" as used herein refers to -C(O)OR in which R is alkyl, preferably loweralkyl or aryl, preferably lower aryl.

20 As used herein, "alkoxy" and "thioalkoxy" refer to RO- and RS-, in which R is alkyl, preferably loweralkyl or aryl, preferably lower aryl.

As used herein, "haloalkoxy" refers to RO- in which R is a haloalkyl group.

As used herein, "aminocarbonyl" refers to -C(O)NH₂.

As used herein, cycloalkyl refers to saturated cyclic carbon chains; cycloalkenyl and cycloalkynyl refer to cyclic carbon chains that include at least one unsaturated triple bond. The cyclic portions of the carbon chains may include one ring or two or more fused rings.

As used herein, alkylenedioxy means an -O-alkyl-O- group in which the alkyl group is as previously described. A replacement analog of alkylenedioxy means an alkylenedioxy in which one or both of the oxygen atoms is replaced by a similar behaving atom or group of atoms such as, S, N, NH, Se. An exemplary replacement alkylenedioxy group is ethylenebis(sulfandiyl). Alkylenethioxyoxy is —S-alkylene-O—, —O-alkylene-S— and alkylenedithioxy is —S-alkylene-S—.

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As used herein, heteroaryl means an aromatic monocyclic or fused ring system in which one or more of the carbon atoms in the ring system is(are) replaced by an element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferred cyclic groups contain one or two fused rings and include from about 3 to about 7 members in each ring. Similar to "aryl groups", the heteroaryl groups may be unsubstituted or substituted by one or more substituents. Exemplary heteroaryl groups include pyrazinyl, pyrazolyl, tetrazolyl, furanyl, (2- or 3-)thienyl, (2-,3- or 4-)pyridyl, imidazolyl, pyrimidinyl, isoxazolyl, thiazolyl, isothiazolyl, quinolinyl, indolyl, isoquinolinyl, oxazolyl and 2,1,3-oxadiazolyl. Preferred heteroaryl groups include 5 to 6-membered nitrogen-containing rings, such as pyrimidinyl.

As used herein, alkoxycarbonyl means an alkyl-O-CO- group. Exemplary alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

As used herein, carbamoyl means -CONH₂. As with all groups described herein, these groups may be unsubstituted or substituted. Substituted carbamoyl includes groups such as -CONY²Y³ in which Y² and Y³ are independently hydrogen, alkyl, cyano(loweralkyl), arylalkyl, heteroaralkyl, carboxy(loweralkyl), carboxy(aryl substituted loweralkyl), carboxy(carboxy substituted loweralkyl), carboxy(hydroxy substituted loweralkyl), carboxy(heteroaryl substituted loweralkyl), carbamoyl(loweralkyl), alkoxycarbonyl(loweralkyl) or alkoxycarbonyl(aryl substituted loweralkyl), provided that only one of Y² and Y³ may be hydrogen and when one of Y² and Y³ is carboxy(loweralkyl), carboxy(aryl substituted loweralkyl), carbamoyl(loweralkyl), alkoxycarbonyl(loweralkyl) or alkoxycarbonyl(aryl substituted loweralkyl) then the other of Y² and Y³ is hydrogen or alkyl. Preferred for Y² and Y³ are independently hydrogen, alkyl, cyano(loweralkyl), arylalkyl, heteroaralkyl, carboxy(loweralkyl), carboxy(aryl substituted loweralkyl) and carbamoyl(loweralkyl).

As used herein, any corresponding N-(4-halo-3-methyl-5-isoxazolyl), N-(4-halo-5-methyl-3-isoxazolyl), N-(3,4-dimethyl-5-isoxazolyl), N-(4-halo-5-methyl-3-isoxazolyl), N-(4-halo-3-methyl-5-isoxazolyl), N-(4,5-dimethyl-3-isoxazolyl) derivative thereof refers to compounds in which Ar² is the same as the compound specifically set forth, but Ar¹ is N-(4-halo-3-methyl-5-isoxazolyl), N-(4-halo-5-methyl-3-isoxazolyl), N-(3,4-dimethyl-5-isoxazolyl), N-(4-halo-5-methyl-3-isoxazolyl), N-(4-halo-3-methyl-5-isoxazolyl), or N-(4,5-dimethyl-3-isoxazolyl) in which halo is any halide, preferably Cl or Br.

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage,

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recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) Biochem. 11:942-944).

A. Nitric oxide (NO) and endothelin

NO, formerly known as endothelium derived relaxing factor, is produced
5 continuously by the lining of blood vessels as a result of the action of an enzyme present in the endothelial cells, endothelial nitric oxide synthase or eNOS. It is thought that eNOS is activated by a rise in intracellular calcium concentration, catalyzing the conversion of L-Arg to NO and L-citrulline. The nitric oxide passes through biological membranes, binds to haem iron in the soluble enzyme guanylate cyclase (GC). The
10 activity of GC is thus stimulated, cyclic guanosine monophosphate concentrations increase and vascular smooth muscle tone is reduced. It has been shown that vascular endothelial cells synthesize nitric oxide from L-arginine (L-Arg) but not D-arginine (see, Palmer, *et al.* (1988) Nature 333:664-666). Release of NO from endothelial cells induced by bradykinin and the calcium ionophore A23187 is reversibly enhanced by
15 infusions of L-Arg or L-citrulline.

The production and release of endothelin from the endothelium is stimulated by angiotensin II, vasopressin, endotoxin, cyclosporine and other factors (see, Brooks *et al.* (1991) Eur. J. Pharm. 194:115-117), and is inhibited by nitric oxide, which was also known as endothelin-derived releasing factor. Hence there appears to be an association
20 between endothelin production and nitric oxide expression.

By virtue of this relationship, as described herein, compounds that modulate the activity, particularly antagonize, endothelin, can be used for treatment of disorders in which NO or related factors is involved.

Laminitis

25 As described herein, methods for treatment of laminitis are provided herein. The methods use endothelin antagonists, particularly sulfonamide compounds and related compounds. As discussed, equine laminitis is has been treated with nitric oxide (NO) NO donors, and a non-steroidal anti-inflammatory drug (NSAID) (see, U.S. Patent No. 5,891,472; see also, Elliott, J. (1996) Equine Vet. J. 28(1):1-2).

30 Menopause and Climacteric disorders

Nitric oxide synthesis and the nitric oxide effector system (cGMP-dependent relation mechanism) are thought to be regulated by steroid hormones. There is an increase in cardiovascular diseases in women following menopause, which may be related to the decrease in sex steroids and an alteration in nitric oxide production.

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Female steroid hormones have been shown to modulate endothelium-dependent relaxation of vascular smooth muscle by nitric oxide. Estradiol treatment of rats causes increased nitric oxide production by vascular tissues, whereas progesterone counteracts this phenomenon (see, e.g., U.S. Patent Nos. 5,906,987, 5,958,878 and 5,898,038).

5 It is also known that pregnancy is associated with an increase in cardiac output and a decrease in the resistance of virtually all the vascular beds in the body. Although the mechanism of this phenomenon is not known, it could be associated with changed in nitric oxide production or effects as a result of elevated steroid hormone levels. One important observation with regard to the above mechanism is that antiprogestins (RU
10 486) elevate blood pressure in animals and they produce hot flushes or flashes in humans, both males and females. The hot flushes or flashes may be mediated by the steroid action on the release of nitric oxide. Hot flushes or flashes are a primary symptom in menopausal and postmenopausal women and they are relieved by both estrogen and progesterone.

15 Another symptom of climacterium in men and women is osteoporosis. There is also growing evidence that nitric oxide mediates steroid (estrogen and/or progestin) effects on bones. There is a need for treatments for climacterium, both male and female, that alleviate the symptoms of progression of the disorders. There is also an increasing need for treatments of menopause and other disorders specific to reduction in
20 hormone levels in postmenopausal women.

Control and management of labor during pregnancy

Spontaneous preterm labor during pregnancy remains an increasing problem confronting the medical community. Preterm labor, whether occurring spontaneously or the one which invariably follows any significant transuterine fetal manipulation such as
25 needle puncture, fetoscopy, or hysterotomy for fetal surgery, presents a serious problem and is a limiting factor for all types of fetal intervention. The severe forms of spontaneous preterm labor or labor induced by an incision in the gravid uterus for open fetal surgery is resistant to all known forms of tocolysis. The management of preterm labor after fetal surgery is particularly difficult and dangerous for mother and fetus
30 because aggressive treatment with magnesium sulfate, betamimetics and other hemodynamically-active tocolytic agents has resulted in sequelae for both mother and fetus.

Tocolytic agents most often used to inhibit preterm labor are β -adrenoreceptor stimulants such as epinephrine or its synthetic analogs and derivatives salbutamol,

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terburtaline, isoxsuprine, ritodrine, and fenoterol, magnesium sulfate, prostaglandin inhibitors such as aspirin, indomethacin and naproxen, ethanol and calcium channel-blocking agents such as nifedipine or nicardipine. However, the potential adverse effects and limited efficacy of these drugs limit their use. Other methods for controlling labor during pregnancy have been reported (see, e.g., U.S. Patent No. 5,830,848).

Modulators of the activity of endothelin peptides

A common feature of the above-noted disorders is the involvement of nitric oxide. It appears to be involved in the etiology and/or pathology of numerous disorders, including laminitis, other inflammatory disorders, and also other disorders, such as menopausal symptoms, pregnancy-related disorders and others. It is shown herein that treatment with endothelin antagonists can ameliorate the symptoms of such disorders. Laminitis is of particular interest herein, but other disorders may be similarly treated.

B. Formulation and administration of the compounds

Compositions for use in the methods herein contain therapeutically effective amounts of one or more endothelin antagonists. The compounds are preferably formulated into suitable pharmaceutical or veterinary preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Preferred compositions include parenteral compositions and transdermal patches. Typically the compounds described above are formulated into pharmaceutical or veterinary compositions using techniques and procedures known in the art (see, e.g., Ansel Introduction to Pharmaceutical Dosage Forms, Fourth Edition 1985, 126).

In the formulations, effective concentrations of one or more compounds or pharmaceutically acceptable derivatives is (are) mixed with a suitable pharmaceutical or veterinary carrier or vehicle. The compounds may be derivatized as the corresponding salts, esters, acids, bases, solvates, hydrates and prodrugs prior to formulation, as described above. The concentrations of the compounds in the formulations are effective for delivery of an amount, upon administration, that ameliorates the symptoms of the endothelin-mediated disease. Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical and veterinary carriers or vehicles suitable for administration of the

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endothelin antagonists include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

In addition, the compounds may be formulated as the sole pharmaceutically or veterinarily active ingredient in the composition or may be combined with other active
5 ingredients. Liposomal suspensions, including tissue-targeted liposomes, may also be suitable as pharmaceutically or veterinarily acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Patent No. 4,522,811.

The active compound is included in the pharmaceutically or veterinarily
10 acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in known in vitro and in vivo systems (see, e.g., the Examples, U.S. Patent No. 5,114,918 to Ishikawa et al.; EP A1 0 436 189 to BANYU PHARMACEUTICAL CO., LTD (October 7,
15 1991); Borges et al. (1989) Eur. J. Pharm. 165:223-230; Filep et al. (1991) Biochem. Biophys. Res. Commun. 177:171-176) and then extrapolated therefrom for dosages for humans.

The concentration of active compound in the drug composition will depend on absorption, inactivation and excretion rates of the active compound, the
20 physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to treat the symptoms of laminitis.

Typically a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/ml to about 50-100 µg/ml. The
25 pharmaceutical and veterinary compositions typically should provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical and veterinary dosage unit forms are prepared to provide from about 1 mg to about 1000 mg and preferably from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

30 The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage

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values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the
5 concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

Preferred pharmaceutically and veterinarily acceptable derivatives include acids, salts, esters, hydrates, solvates and prodrug forms. The derivative is selected such that its pharmacokinetic properties are superior to the corresponding neutral compound.

10 Thus, effective concentrations or amounts of one or more of the compounds provided herein or pharmaceutically or veterinarily acceptable derivatives thereof are mixed with a suitable pharmaceutical or veterinary carrier or vehicle for systemic, topical or local administration to form pharmaceutical or veterinary compositions. Compounds are included in an amount effective for ameliorating or treating the endothelin-mediated
15 disorder for which treatment is contemplated. The concentration of active compound in the composition will depend on absorption, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

The compositions are intended to be administered by a suitable route, which
20 includes orally, parenterally, rectally and topically and locally depending upon the disorder being treated. For oral administration, capsules and tablets are presently preferred. The compounds in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. Preferred modes of administration include parenteral, oral and topical modes of administration.

25 Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating
30 agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

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In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using co-solvents, such as dimethylsulfoxide (DMSO), using surfactants, such as Tween®, or dissolution in aqueous sodium

5 bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical and veterinary compositions.

Upon mixing or addition of the compound with the vehicle, the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and
10 the solubility of the compound in the selected carrier or vehicle. If necessary, pharmaceutically or veterinarily acceptable salts or other derivatives of the compounds may be prepared.

The compound is included in the pharmaceutically or veterinarily acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of
15 undesirable side effects on the patient treated. It is understood that number and degree of side effects depends upon the condition for which the compounds are administered. For example, certain toxic and undesirable side effects are tolerated when treating life-threatening illnesses, such as tumors, that would not be tolerated when treating disorders of lesser consequence. The concentration of compound in the composition will
20 depend on absorption, inactivation and excretion rates thereof, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the
25 solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

The formulations are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral
30 solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The pharmaceutically or veterinarily therapeutically active compounds and derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to

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physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical or veterinary carrier, vehicle or diluent.

- 5 Examples of unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or
10 gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

- The composition can contain along with the active ingredient: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural
15 gums, such as gum acaciagelatin, glucose, molasses, polvinylpyrrolidine, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically and veterinarily administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical or veterinary adjuvants in a
20 carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical or veterinary composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine
25 derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity
30 of the active compound in an amount sufficient to alleviate the symptoms of the treated subject.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically or veterinarily acceptable non-toxic

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composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, 5 suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these formulations are known to those skilled in the art. The contemplated 10 compositions may contain 0.001%-100% active ingredient, preferably 0.1-85%, typically 75-95%.

The active compounds or pharmaceutically or veterinarily acceptable derivatives may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings.

15 The formulations may be include other active compounds to obtain desired combinations of properties. The compounds or pharmaceutically or veterinarily acceptable derivatives thereof as described herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of 20 the diseases or medical conditions referred to hereinabove, such as beta-adrenergic blocker (for example atenolol), a calcium channel blocker (for example nifedipine), an angiotensin converting enzyme (ACE) inhibitor (for example lisinopril), a diuretic (for example furosemide or hydrochlorothiazide), an endothelin converting enzyme (ECE) inhibitor (for example phosphoramidon), a neutral endopeptidase (NEP) inhibitor, an 25 HMGCoA reductase inhibitor, a nitric oxide donor, an anti-oxidant, a vasodilator, a dopamine agonist, a neuroprotective agent, a steroid, a beta-agonist, an anti-coagulant, or a thrombolytic agent. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

30 **1. Injectables, solutions and emulsions**

Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions.

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Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical or veterinary compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, e.g., U.S. Patent No. 3,710,795) is also contemplated herein. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

Parenteral administration of the formulations includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as the lyophilized powders described herein, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

Pharmaceutically or veterinarily acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically or veterinarily acceptable substances.

Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium

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chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (Tween® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical or veterinary carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of the pharmaceutically or veterinarily active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

The unit-dose parenteral preparations are packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

Illustratively, intravenous or intra-arterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

Injectables are designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

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The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or
5 vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

2. Topical administration

Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the
10 like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration. Transdermal patches are of particular interest herein (see, e.g., U.S. Patent No. 5,891,472).

15 The compounds or pharmaceutically or veterinarily acceptable derivatives thereof may be formulated as aerosols for topical application, such as by inhalation (see, e.g., U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an
20 aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically diameters of less than 50 microns, preferably less than 10 microns.

The compounds may be formulated for local or topical application, such as for
25 topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically
30 acceptable excipients can also be administered.

These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

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3. Formulations for oral administration

Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated
5 or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

In certain embodiments, the formulations are solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of
10 the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents
15 include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved
20 certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as sodium cyclamate and saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant
25 sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000
30 and cellulose acetate phthalate.

If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in

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the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can
5 contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

10 The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action. For example, if the compound is used for treating laminitis, it may be used with other such treatments, such as a nitric oxide donor or a nitric oxide synthase substrate. The active ingredient is a compound or pharmaceutically or veterinarily acceptable derivative
15 thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

Pharmaceutically or veterinarily acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating,
20 resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one
25 compression cycle utilizing the pharmaceutically or veterinarily acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar-coated, multiple compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

30 Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

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Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically or veterinarily acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically or veterinarily acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically or veterinarily acceptable suspending agents and preservatives. Pharmaceutically or veterinarily acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically or veterinarily acceptable substance used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as sodium cyclamate and saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Patent Nos 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, e.g., in a polyethylene glycol, may be diluted with a sufficient quantity of a

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pharmaceutically or veterinarily acceptable liquid carrier, e.g., water, to be easily measured for administration.

Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (e.g., propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. Re 28,819 and 4,358,603.

In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

4. Lyophilized powders

Also of interest herein are lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be formulated as solids or gels.

Pharmaceutical and veterinary compositions of salts of the active ingredients, particularly sodium hydrogen phosphate or sodium, preferably sodium, salts of the sulfonamide compounds, which possess increased stability relative to formulations of the neutral sulfonamides are of interest herein. Such compositions contain a sulfonamide sodium salt in a sterile, lyophilized powder. These powders are known to have increased stability relative to formulations of the neutral sulfonamides.

The sterile, lyophilized powder is prepared by dissolving the sodium salt in a sodium phosphate buffer solution containing dextrose or other suitable excipient. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Briefly, the lyophilized powder is prepared by dissolving dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent, about 1-20%, preferably about 5 to 15%, in a suitable buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, typically, about neutral pH. Then, a selected salt, preferably the sodium salt of the sulfonamide (about 1 g of the salt per 10-100 g of the buffer solution, typically about 1 g/30 g), is added to the resulting mixture, preferably above room temperature, more preferably at about 30-35° C, and stirred until it dissolves. The resulting mixture is diluted by adding more

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buffer (so that the resulting concentration of the salt decreases by about 10-50%, typically about 15-25%). The resulting mixture is sterile filtered or treated to remove particulates and to insure sterility, and apportioned into vials for lyophilization. Each vial will contain a single dosage (100-500 mg, preferably 250 mg) or multiple dosages of the sulfonamide salt. The lyophilized powder can be stored under appropriate conditions, such as at about 4° C to room temperature.

Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration of sodium salts of the sulfonamides. For reconstitution about 1-50 mg, preferably 5-35, more preferably about 9-30 is added per ml of sterile water or other suitable carrier. The precise amount depends upon the indication treated and selected compound. Such amount can be empirically determined.

5. Formulations for other routes of administration

Depending upon the condition treated other routes of administration, such as rectal administration are also contemplated herein.

For example, pharmaceutical and veterinary dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax, (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 g.

Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

30 C. Compounds for pharmaceutical or veterinary use in treating endothelin-mediated diseases

Provided herein are methods for the treatment of inflammatory diseases, particularly, laminitis, and other diseases that can be treated by increasing levels of nitric oxide. The methods are practiced by administering an effective amount of an

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endothelin antagonist, particularly, a sulfonamide. Numerous endothelin antagonists and sulfonamide endothelin antagonists are known (see, e.g., U.S. Patent Nos. 6,133,442, 6,133,263, 6,107,320, 6,083,955; 6,083,951; 6,080,774; 6,063,911; 6,060,475; 6,043,265; 6,043,241; 6,030,991; 6,017,951; 6,017,916; 6,013,655; 5 6,004,965; 5,965,732; 5,962,682; 5,958,968; 5,948,754; 5,945,448; 5,942,516; 5,929,116; 5,929,106; 5,925,731; 5,922,759; 5,922,681; 5,891,892; 5,888,972; 5,883,092; 5,883,090; 5,883,075; 5,866,568; 5,861,401; 5,856,484; 5,840,722; 5,837,708; 5,834,469; 5,821,256; 5,817,693; 5,817,683; 5,817,653; 5,811,444; 5,811,416; Re35,886; 5,780,498; 5,773,444; 5,773,414; 5,767,310; 5,767,144; 10 5,753,619; 5,739,333; 5,736,564; 5,731,434; 5,731,321; 5,728,706; 5,726,194; 5,719,183; 5,719,182; 5,716,985; 5,716,984; 5,714,479; 5,703,106; 5,700,807; 5,691,373; 5,691,315; 5,688,974; 5,688,499; 5,686,481; 5,686,478; 5,668,176; 5,668,137; 5,663,296; 5,658,943; 5,658,902; 5,656,604; 5,654,309; 5,641,793; 5,641,752; 5,622,971; 5,616,684; 5,614,498; 5,614,497; 5,610,177; 5,608,078; 15 5,599,811; 5,591,728; 5,939,446; 5,916,907; 5,856,507; 5,846,990; 5,846,985; 5,827,869; 5,780,473; 5,760,038; 5,378,715; 5,514,696; 5,420,123; 5,612,359; 5,543,521; 5,464,853; 5,514,691; 5,292,740; 5,334,598; 5,571,821; 5,389,620; 5,541,186; 5,559,105; and 5,482,960; European Patent Application Nos. EP 959073; EP 959072; EP 929529; EP 925297; EP 924207; EP 916679; EP 915699; EP 906108; 20 EP 904077; EP 901470; EP 888340; EP 888299; EP 888123; EP 885890; EP 885219; EP 885217; EP 885215; EP 882039; EP 882030; EP 874829; EP 873334; EP 868180; EP 863898; EP 863896; EP 861247; EP 857718; EP 854721; EP 852584; EP 852226; EP 846119; EP 844884; EP 843551; EP 841926; EP 841925; EP 841916; EP 838223; EP 832082; EP 830143; EP 821670; EP 817782; EP 811001; EP 805802; EP801062; 25 EP 799221; EP 799209; EP 799206; EP 792265; EP 790993; EP 778833; EP 776324; EP 774965; EP 768878; EP 768304; EP 767801; EP 767794; EP 766684; EP 763035; EP 758650; EP 757039; EP 755934; EP 753004; EP 752986; EP 898571; EP 889894; EP 870764; EP 876364; EP 819125; EP 528312; EP 552489; EP 499266; EP 457195; EP 460679; EP 626174; EP 558258; EP 569193; EP 768305; EP 904077; EP 921800; 30 EP 702012; EP 601386; EP 633259; EP 510526; EP 526708; EP 617001; EP 496452; EP 658548; EP 555537; EP 628569; EP 552417; EP 436189; EP 713875; EP 733626; EP 682016; and EP 743307; British Patent Application Nos. GB 2276383; GB 2275926; GB 2266890; GB 2277446; and GB 2295616; German Patent Application No. DE 4341663; Japanese Patent Application Nos. 4-288099; 5-178890; 5-279390;

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5 Patent Application Publication Nos. WO 99/44988; WO 99/42453; WO 99/36408; WO 99/29685; WO 99/27934; WO 99/25701; WO 99/23078; WO 99/20623; WO 99/19346; WO 99/19320; WO 99/16445; WO 99/12916; WO 99/11629; WO 99/06397; WO 99/05132; WO 99/02519; WO 98/58916; WO 98/57938; WO 98/57933; WO 98/41521; WO 98/41515; WO 98/41206; WO 98/27091; WO

10 98/27070; WO 98/09953; WO 98/08836; WO 97/47595; WO 97/43260; WO 97/37987; WO 97/37986; WO 97/37985; WO 97/33608; WO 97/30996; WO 97/30982; WO 97/30978; WO 97/30046; WO 97/30045; WO 97/28160; WO 97/28159; WO 97/28158; WO 97/28154; WO 97/22341; WO 97/21700; WO 97/19077; WO 97/17340; WO 97/17339; WO 97/17071; WO 97/12878; WO

15 97/11961; WO 97/11960; WO 97/11942; WO 97/10214; WO 97/08169; WO 97/07119; WO 97/04781; WO 97/04774; WO 97/04773; WO 97/04772; WO 97/04769; WO 97/02265; WO 91/13089; WO 92/12991; WO 97/39000; WO 92/20706; WO 93/13218; WO 93/17701; WO 98/33780; WO 98/04260; WO 97/33886; WO 97/29748; WO 97/29747; WO 94/27979; WO 97/25321; WO

20 97/35864; WO 96/06095; WO 95/08550; WO 95/26716; WO 96/11914; WO 95/26360; WO 93/25580; WO 93/23404; WO 96/04905; WO 94/21259; WO 95/03044; WO 95/03295; WO 95/08989; WO 94/21590; WO 94/21259; WO 95/13262; WO 96/12706; WO 94/24084; WO 94/25013; WO 95/04534; WO 95/04530; WO 94/02474; WO 94/14434; WO 96/07653; WO 93/08799; WO

25 95/05376; WO 95/12611; WO 95/15963; WO 95/15944; WO 95/05374; WO 95/05372; WO 94/03483; WO 93/21219; WO 96/11927; WO 96/23773; WO 96/33170; WO 96/15109; WO 96/33190; WO 96/19459; WO 96/19455; WO 95/26360; WO 96/20177; WO 96/08486; WO 96/09818; WO 96/08487; WO 96/04905; WO 96/22978; WO 96/08483; WO 95/33748; WO 96/30358; WO

30 95/35107; WO 95/26957; WO 95/33752; and WO 96/31492; commonly owned U.S. Patent application Serial Nos. 08/721,183; 08/938,325; 08/938,444; 08/730,633; 09/148,643; 09/274,280; and 08/913,331; such as the following compounds described in the recited documents: BQ-123 (Ihara, M., et al., Biological Profiles of Highly Potent Novel Endothelin Antagonists Selective for the ET_A Receptor, *Life*

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- Sciences*, 50(4):247-255 (1992)); PD 156707 (Reynolds, E., et al., Pharmacological Characterization of PD 156707, an Orally Active ET_A Receptor Antagonist, *The Journal of Pharmacology and Experimental Therapeutics*, 273(3):1410-1417 (1995)); L-754,142 (Williams, D. L., et al., Pharmacology of L-754,142, a Highly Potent, Orally
- 5 Active, Nonpeptidyl Endothelin Antagonist, *The Journal of Pharmacology and Experimental Therapeutics*, 275(3):1518-1526 (1995)); SB 209670 (Ohlstein, E. H., et al., SB 209670, a rationally designed potent nonpeptide endothelin receptor antagonist, *Proc. Natl. Acad. Sci. USA*, 91:8052-8056 (1994)); SB 217242 (Ohlstein, E. H., et al., Nonpeptide Endothelin Receptor Antagonists. VI: Pharmacological Characterization of SB
- 10 217242, A Potent and Highly Bioavailable Endothelin Receptor Antagonist, *The Journal of Pharmacology and Experimental Therapeutics*, 276(2):609-615 (1996)); A-127722 (Opgenorth, T. J., et al., Pharmacological Characterization of A-127722: An Orally Active and Highly Potent ET_A-Selective Receptor Antagonist, *The Journal of Pharmacology and Experimental Therapeutics*, 276(2):473-481 (1996)); TAK-044
- 15 (Masuda, Y., et al., Receptor Binding and Antagonist Properties of a Novel Endothelin Receptor Antagonist, TAK-044 {Cyclo[D- α -Aspartyl-3-[(4-Phenylpiperazin-1-yl)Carbonyl]-L-Alanyl-L- α -Aspartyl-D-2-(2-Thienyl)Glycyl-L-Leucyl-D-Tryptophyl]Disodium Salt}, in Human Endothelin_A and Endothelin_B Receptors, *The Journal of Pharmacology and Experimental Therapeutics*, 279(2):675-685 (1996)); bosentan (Ro 47-0203, Clozel, M.,
- 20 et al., Pharmacological Characterization of Bosentan, A New Potent Orally Active Nonpeptide Endothelin Receptor Antagonist, *The Journal of Pharmacology and Experimental Therapeutics*, 270(1):228-235 (1994)), and many are described herein.

In one embodiment, the endothelin receptor antagonists for use in the methods provided herein have formula I:

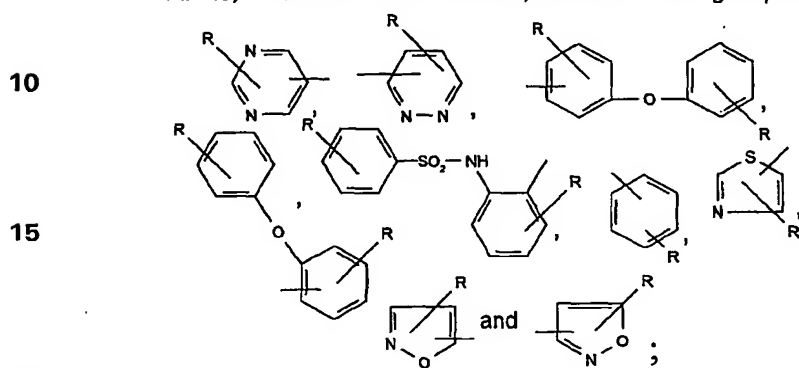


- 30 or a pharmaceutically or veterinarily acceptable derivative thereof, in which Ar¹ is alkyl, alkenyl, or alkynyl, or is a substituted or unsubstituted aryl or heteroaryl group that, if substituted, is substituted with one or more substituents, including, but not limited to, an alkyl group, an aryl group, a substituted aryl group, a nitro group, an amino group or a halide. In particular, Ar¹ is alkyl, alkenyl, or alkynyl, or is a five or six membered
- 35 substituted or unsubstituted aromatic or heteroaromatic ring, including, but not limited to, isoxazolyl, including 3- or 5- isoxazolyl, pyridazinyl, thiazolyl, including 2-thiazolyl,

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pyrimidinyl, including 2-pyrimidinyl, pyrazolyl, isothiazolyl, including 3- or 5-isothiazolyl, pyrazinyl, or a substituted benzene group, including aryloxy substituted benzene groups or is a fused aliphatic or heteroaliphatic ring containing from 6 to about 21 carbons in the ring structure, such as bicyclic or tricyclic rings, including naphthyl groups, quinolyl groups, dibenzofuryl groups, dibenzopyrrolyl groups, dibenzothienyl groups, purines, and phenanthrenes.

Ar¹ is, in certain embodiments, selected from groups such as:



that are unsubstituted or substituted with one or more substituents selected from R. R is selected from H, NH₂, halide, pseudohalide, alkyl alkylcarbonyl, formyl, an aromatic or heteroaromatic group, alkoxyalkyl, alkylamino, alkylthio, arylcarbonyl, aryloxy, arylamino, arylthio, haloalkyl, haloaryl and carbonyl, in which the aryl and alkyl portions are unsubstituted or substituted with any of the preceding groups, and is unsubstituted or substituted with any of the preceding groups, and straight or branched chains of from about 1 up to about 10-12 carbons, preferably, 1 to about 5 or 6 carbons. R is preferably H, NH₂, halide, CH₃, CH₃O or another aromatic group.

Ar² is any group such that the resulting sulfonamide inhibits binding by 50%, compared to binding in the absence of the sulfonamide, of an endothelin peptide to an endothelin receptor at a concentration of less than about 100 μM. In certain embodiments herein, Ar² is selected with the proviso that Ar² is not phenyl or naphthyl when Ar¹ is N-(5-isoxazolyl) or N-(3-isoxazolyl) unless the isoxazole is a 4-halo-isoxazole or, if enhanced ET_B affinity is desired, a 4-higher alkyl-isoxazole, and when Ar² is phenyl it is not substituted at the para position with NH₂, NO₂, CH₃, OH or a substituted amine.

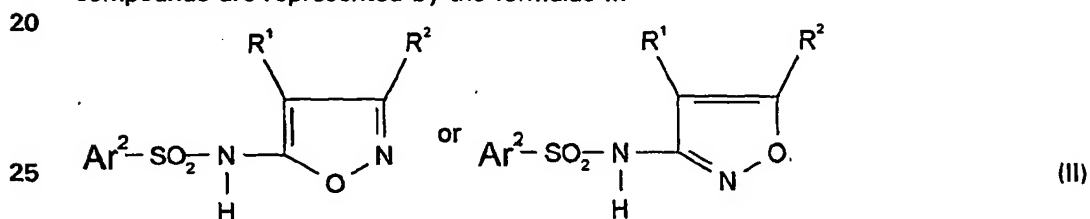
Selected isoxazolyl-benzenesulfonamides and isoxazolyl-naphthalenesulfonamides in which the isoxazole is other than a 4-halo-isoxazole are also provided. Such selected compounds, including N-isoxazolylbenzenesulfonamides and N-isoxazolynaphthalenesulfonamides in which the substituent at the 4 position on the

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isoxazolyl group is higher alkyl, such as C_9H_{19} to $C_{13}H_{27}$ are also provided. These compounds enhanced ET_B affinity compared to corresponding compounds in which the substituent at the 4 position is lower alkyl or other groups, such as pseudohalide, halide, alkylaryl, aryl, lower alkyl, carboxamide, alkoxy, and others.

- 5 Thus, Ar^2 is selected from among alkyl, including straight and branched chains, aromatic rings, fused aromatic rings and heterocyclic rings, including, 5-membered heterocycles with one, two or more heteroatoms and fused ring analogs thereof and 6-membered rings with one, two or more heteroatoms and fused ring analogs thereof. Ar^2 , thus, includes, but is not limited to, alkyl, norboranyl, adamantyl, phenyl, naphthyl, 10 quinolyl, isoquinolyl, acridinyl, styryl, biphenyl, isoxazolyl, thiazolyl, oxazolyl, imidazole, dibenzofuryl, indolyl (dibenzopyrrolyl), dibenzothieryl (thianaphthalene), carbazolyl, purinyl, and phenanthryl, anthracenyl, furyl, pyrrolyl, thienyl, imidazolyl, oxazolyl, pyrazolyl, pyrrolidinyl, pyrrolinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyradazinyl, morpholinyl, thiomorpholinyl, quiniolizolonyl, quiniolxazinyl, phthalazinyl, cinnolinyl, 15 phenazinyl, phenoxzainyl, phenothiazinyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, and the like. In preferred embodiments herein, Ar^2 is phenyl, naphthyl, furyl, pyrrolyl, thienyl, biphenyl, and thiadazolyl.

In the embodiments described in detail herein, Ar^1 is an isoxazole and the compounds are represented by the formulae II:



- or pharmaceutically or veterinarily acceptable derivatives thereof, in which R^1 and R^2 are either (i), (ii) or (iii) as follows:

- (i) R^1 and R^2 independently selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, hydroxyalkyl, alkoxyalkyl, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, 35 alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido and substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons; or,

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(ii) R^1 and R^2 together form $-(CH_2)_n$, where n is 3 to 6; or,

(iii) R^1 and R^2 together form 1,3-butadienyl.

In certain embodiments, the compounds are selected with the proviso that R^2 is not halide or pseudohalide. In other embodiments, the compounds are selected with the
 5 proviso that Ar^2 is not phenyl or naphthyl unless R^1 is a halide or a higher alkyl, particularly C_9H_{19} to $C_{13}H_{27}$.

In preferred embodiments herein, R^1 is selected from alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, halide, and pseudohalide; and R^2 is selected from among lower alkyl, lower alkenyl, lower alkynyl and lower haloalkyl.

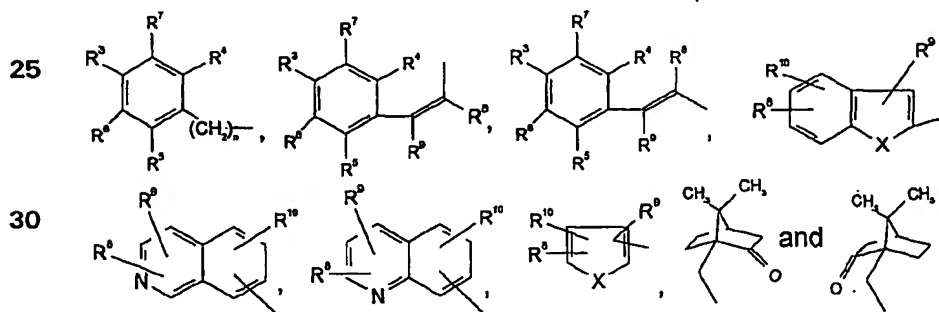
10 Ar^2 is any group such that the resulting sulfonamide inhibits binding by 50%, compared to binding in the absence of the sulfonamide, of an endothelin peptide to an endothelin receptor at a concentration of less than about 100 μM .

In certain embodiments, Ar^2 is not phenyl or naphthyl unless the compound is an N-isoxazolylsulfonamide substituted at the 4-position on the isoxazoly group with halide
 15 or higher alkyl, particularly C_9H_{19} to $C_{13}H_{27}$.

In particular, Ar^1 is an isoxazoly group, and Ar^2 is an aliphatic straight or branched carbon chain, including alkyl, alkenyl, and alkynyl groups, heterocycle, with one or more, generally one to three rings, or is a group or isomer group selected.

In other embodiments, Ar^2 is not phenyl or naphthyl, unless R^1 (the 4-substituent
 20 on the isoxazoly group (Ar^1)) is a halide or a higher alkyl, with greater than 8 carbons, preferably C_9H_{19} to $C_{13}H_{27}$.

Ar^2 is in certain embodiments selected from among groups including: alkyl,



35 in which n is 0 to 10, preferably 0 to 6, more preferably 0 to 3; X is O, S or NR^{11} , where R^{11} , which is hydrogen or contains up to about 30 carbon atoms, generally 1 to 16 carbon atoms, and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{15}$ and

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- S(O)_nR¹⁵ in which n is 0-2; R¹⁵ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R¹¹ and R¹⁵ are unsubstituted or are substituted with one or more substituents each selected independently from Z, which is halide, pseudoalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁶, CO₂R¹⁶, SH, S(O)_nR¹⁶ in which n is 0-2, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶; R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹², which is selected independently from R¹¹ and Z, is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2; and R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R¹¹, R¹², R¹⁵ and R¹⁶ may be further substituted with the any of the groups set forth for Z;
- R³, R⁴, R⁵, R⁶ and R⁷ are each selected independently from (i)-(iv);
- (i) R³, R⁴, R⁵, R⁶ and R⁷ are each selected independently from among H, NHOH, NH₂, NO₂, N₃, aminoalkyl, alkylamino, dialkylamino, carboxyl, carbonyl, hydroxyl, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, heterocycle, alkoxy, alkylthio, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylalkoxy, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, haloalkoxy, alkoxy carbonyl, alkyl carbonyl, aryl carbonyl, formyl, substituted or unsubstituted amido and substituted or unsubstituted ureido in which each of the preceding groups may be unsubstituted or substituted with groups such as H, NH₂, NO₂, alkyl, halide, and pseudohalide; or, alternatively,
- (ii) R⁴ and R⁷ together are substituted or unsubstituted 1, 3-butadienyl, 1-chloro-1,3-butadienyl, 4-dimethylamino-1,3-butadienyl, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R³, R⁵ and R⁶ are as defined in (i) above; or alternatively,
- (iii) R⁷ and R³ together are substituted or unsubstituted 1, 3-butadienyl, 4-dimethylamino-1,3 butadienyl, 1-chloro-1,3-butadienyl, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R⁴, R⁵ and R⁶ are as defined in (i) above; or alternatively,
- (iv) R³, R⁵, and R⁷ are H; and R⁴ and R⁶ are each independently selected from alkyl, alkoxy, halide, amino and aminoalkyl; and
- R⁸, R⁹, R¹⁰ are each independently selected as follows from (i) or (ii):
- (i) R⁸, R⁹ and R¹⁰, which each contain hydrogen or up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, are each independently selected from hydrogen, halide pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy,

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heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁸, CO₂R¹⁸, SH, S(O)_nR¹⁸ in which n is 0-2, HNOH, NR¹⁸R¹⁹, NO₂, N₃, OR¹⁸, R¹⁹NCOR¹⁸ and CONR¹⁹R¹⁸, in which R¹⁹ is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²⁰, S(O)_nR²⁰ in which n is 0-2; and R¹⁸ and R²⁰ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; and any of the groups set forth for R⁸, R⁹ and ¹⁰ are unsubstituted or substituted with any substituents set forth for Z, which is halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R²¹, CO₂R²¹, SH, S(O)_nR²¹ in which n is 0-2, NHOH, NR²²R²¹, NO₂, N₃, OR²¹, R²²NCOR²¹ and CONR²²R²¹; R²² is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²³ and S(O)_nR²³ in which n is 0-2; and R²¹ and R²³ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; or

(ii) any two of R⁸, R⁹ and R¹⁰ form an aryl, aromatic ring, heteroaromatic ring, alicyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to 7 members that is unsubstituted or substituted with one or more substituents in each each substituent is independently selected from Z; and the other of R⁸, R⁹ and R¹⁰ is selected as in (i).

In certain embodiments, when Ar² is phenyl (a) at least one of R³, R⁴, R⁵, R⁶, and R⁷ is not hydrogen and (b) when Ar¹ is 3-isoxazolyl, R³ is not NH₂ or CH₃.

In the above embodiments, the alkyl, alkynyl and alkenyl portions of each listed substituent are straight or branched chains, acyclic or cyclic, and preferably have from about 1 up to about 10 carbons; in more preferred embodiments they have from 1-6 carbons, and they can have fewer than 6 carbons. The aryl, alicyclic, aromatic rings and heterocyclic groups can have from 3 to 16, generally, 3-7, more often 5-7 members in the rings, and may be single or fused rings. The ring size and carbon chain length are selected up to an amount that the resulting molecule binds to retains activity as an endothelin antagonist or agonist, such that the resulting compound inhibits binding by 50%, compared to binding in the absence of the sulfonamide, of an endothelin peptide

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to an endothelin receptor at a concentration of less than about 50 μM , preferably less than about 10 μM .

Thus, Ar^2 is a substituted or unsubstituted group selected from among groups such as the following: naphthyl, phenyl, biphenyl, quinolyl, styryl, thienyl, furyl, isoquinolyl, pyrrolyl, benzofuranyl, benzothienyl, benzopyrrolyl, pyridinyl, thianaphthalyl, indolyl, dibenzofuranyl, dibenzopyrrolyl, dibenzothienyl, phenanthryl, thiazolyl, isoxazolyl, anthacenyl, alkenyl, alkynyl and alkyl. It is understood that the positions indicated for substituents, including the sulfonamide groups, may be varied. Thus, for example, compounds herein encompass groups that include thiophene-3-sulfonamides and thiophene-2-sulfonamides.

In embodiments described in detail herein, Ar^1 is isoxazolyl. In all embodiments, 4-haloisoxazolyl or 4-methylisoxazolyl are preferred, except when Ar^2 is phenyl or naphthyl, then 4-haloisoxazolyl and 4-higher alkylisoxazolyl are preferred. In general, 4-haloisoxazolyl sulfonamides exhibit substantially enhanced activity with respect to at least one of the ET_A receptors (about two-fold to twenty-fold greater activity), as assessed by assays, such as those provided herein, that measure binding to ET_A and/or ET_B receptors, compared to corresponding sulfonamides in which the substituent at the 4 position in the isoxazolyl is other than halo, such as alkyl. For example: (1) the IC_{50} for competitive inhibition of binding of ET-1 to ET_A receptors of 2,5-dimethyl-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide is 9.4 μM ; whereas the IC_{50} for 2,5-dimethyl-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide is 0.19 μM and for 2,5-dimethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide is 0.044 μM ; (2) the IC_{50} of N-(3,4-dimethyl-5-isoxazolyl)-2-biphenylsulfonamide for ET_A receptors is about 0.008 μM , whereas, the IC_{50} of N-(4-bromo-3-methyl-5-isoxazolyl)-2-biphenylsulfonamide is about 0.0016 μM ; and (3) the IC_{50} of N-(3,4-dimethyl-5-isoxazolyl)-3-biphenylsulfonamide for ET_B receptors is about 3.48 μM ; whereas, the IC_{50} of N-(4-bromo-3-methyl-5-isoxazolyl)-3-biphenylsulfonamide for ET_B receptors is about 0.76 μM and the IC_{50} of N-(4-chloro-3-methyl-5-isoxazolyl)-3-biphenylsulfonamide for ET_B receptors is about 0.793 μM (see, the Tables).

Other selected compounds include benzene and naphthalene isoxazole sulfonamides in which the 4 position on the isoxazole ring of Ar^1 is a methyl group and the 3 position is a relatively long chain (greater than about 8 carbons up to about 15 carbons, preferably about 13 carbons) alkyl group. Such compounds, although reportedly exhibiting a loss in affinity to ET_A receptors (see, Stein *et al.* (1994) *J. Med.*

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Chem. 37:329-331), are herein shown to exhibit increased affinity to ET_B receptors compared to compounds in which the group at the 3 position is a methyl group.

In certain preferred embodiments herein, R¹¹ is aryl, such as phenyl, alkylphenyl, hydrogen or lower alkyl, and R⁸, R⁹, R¹⁰ are independently selected from hydrogen, halide, lower alkyl, lower aralkyl, lower heterocycle, lower aralkyl, C(O)₂R¹⁸, CO₂R¹⁸, NO₂, OR¹⁸ SR¹⁸, NR¹⁸COR¹⁹ or CONR¹⁹R¹⁸; R¹⁸ and R¹⁹ are preferably hydrogen, lower alkyl, and lower aryl, and Z is hydrogen, halide, pseudohalide, lower alkyl, lower alkoxy or pseudohalo- or halo(lower)alkyl. In certain more preferred embodiments, R⁸ and R¹⁰ are hydrogen, halide or methyl, more preferably hydrogen or halide, and R⁹ is selected independently from hydrogen, halide, aryl, pseudohalide, lower alkyl, preferably methyl or ethyl, COR¹⁸, CONR¹⁸R¹⁹ and NR¹⁸COR¹⁹.

In the preferred compounds herein, R² is preferably, selected from among alkyl, lower alkenyl, lower alkynyl, lower haloalkyl or H; and R¹ is halide, lower alkyl or lower haloalkyl, and more preferably, R¹ is bromide, chloride, methyl or ethyl. In the most active compounds provided herein, as evidenced by in vitro binding assays, R¹ is bromide or chloride.

In preferred embodiments herein, the compounds have formula II in which R¹ is halide or methyl, R², Ar², R³, R⁵, R⁶, R⁸, R⁹, R¹⁰ and R¹¹ are as defined above. In most preferred embodiments, R¹ is bromide, chloride or methyl. Thus, in general, the most preferred compounds herein, particularly with respect to ET_A affinity, are N-(4-bromo, chloro, or methylisoxazolyl)sulfonamides. Compounds in which R¹ is methyl and Ar² is other than phenyl or naphthyl are also preferred.

Preferred compounds also include compounds that are ET_B receptor selective or that bind to ET_B receptors with an IC₅₀ of less than about 1 μM. In these compounds, Ar² is 3-biphenyl, 4-biphenyl, certain compounds in which Ar² phenanthrene or is a 5-membered heterocycle, particularly thienyl, compounds in which Ar² is naphthyl and phenyl and R¹ is higher alkyl (C₉H₁₉ to C₁₃H₂₇). R² is selected from among alkyl, lower haloalkyl and H; and R¹ is halide, lower alkyl or lower haloalkyl, or, when Ar² is phenyl or naphthyl, R¹ is higher alkyl (nine or more carbon atoms, preferably 9 to 13 carbon atoms). The 5-membered heterocyclic compounds that exhibit ET_B affinity or selectivity are those in which R⁹ and R¹⁰ are selected independently from hydrogen, lower alkyl, preferably methyl or ethyl, and halide, and R⁸, which is the substituent at the 5-position (see, e.g., the formulae setting forth the numbering for the 5-membered heterocyclic

ring compounds), is aryl or a heterocycle, particularly phenyl and isoxazolyl, which are unsubstituted or substituted with Z, which is preferably lower alkyl or halide.

Also among the most preferred compounds for use in methods provided herein, are those that are ET_A selective, *i.e.*, they interact with ET_A receptors at concentrations
 5 at substantially lower concentrations (at an IC_{50} at least about 10-fold lower, preferably 100-fold lower) than they interact with ET_B receptors. Other preferred compounds are ET_B selective. These compounds interact with ET_B receptors at IC_{50} concentrations that are at least about 10-fold lower than the concentrations at which they interact with ET_A receptors. In particular, compounds that interact with ET_A with an IC_{50} of less than
 10 about 10 μM , preferably less than 1 μM , more preferably less than 0.1 μM , but with ET_B with an IC_{50} of greater than about 10 μM or compounds that interact with ET_B with an IC_{50} of less than about 10 μM , preferably less than 1 μM , more preferably less than 0.1 μM , but with ET_A with an IC_{50} of greater than about 10 μM are preferred.

Among others of the preferred compounds for use in the methods herein are any
 15 compounds that interact with ET_A and/or ET_B receptors with an IC_{50} of less than about 10 μM , more preferably less than 1 μM , even more preferably less than about 0.1 μM , even more preferably less than about 0.01 μM and most preferably less than about 0.001 μM .

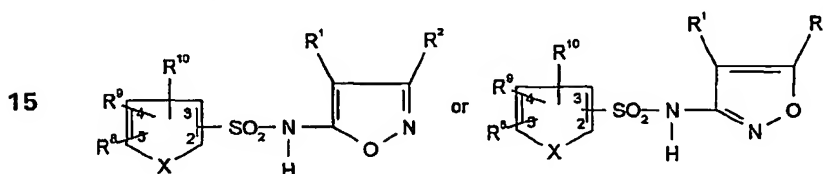
In certain embodiments described in detail herein, Ar^2 is a 4-biphenyl or is a
 20 single ring heterocycle, particularly a 5-membered ring, or is a fused bicyclic or tricyclic heterocycle that contains one or more, particularly one, heteroatom selected from S, O and NR^{42} , in the ring, where R^{42} contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl,
 25 $C(O)R^{16}$ and $S(O)_nR^{16}$ in which n is 0-2; R^{16} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R^{42} and R^{16} are unsubstituted or are substituted with one or more substituents each selected independently from Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH,
 30 CN, $C(O)R^{16}$, CO_2R^{16} , SH, $S(O)_nR^{16}$ in which n is 0-2, $NHOH$, $NR^{12}R^{16}$, NO_2 , N_3 , OR^{16} , $R^{12}NCOR^{16}$ and $CONR^{12}R^{16}$; R^{16} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R^{12} , which is selected independently from R^{42} and Z, is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cyclo-

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alkynyl, $C(O)R^{17}$ and $S(O)_nR^{17}$ in which n is 0-2; and R^{17} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R^{42} , R^{12} , R^{15} and R^{16} may be further substituted with the any of the groups set forth for Z .

- 5 In preferred embodiments herein, R^{42} is aryl, such as phenyl or alkyl phenyl, hydrogen or loweralkyl.

Thus, in the compounds provided herein Ar^2 includes thienyl, furyl and pyrrolyl, benzofuryl, benzopyrrolyl, benzothienyl, benzo[b]furyl, benzo[b]thienyl, and indolyl (benzo[b]pyrrolyl) and 4-biphenyl, and Ar^1 is preferably N-(5-isoxazolyl) or N-(3-isoxazolyl). The sulfonamides are N-isoxazolyl sulfonamides and the compounds have
 10 have formula III:

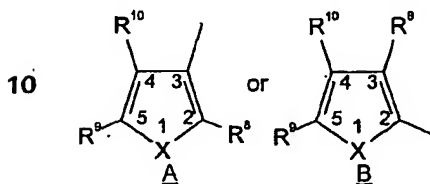


- 20 in which X is S, O or NR^{11} in which R^{11} contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{15}$ and $S(O)_nR^{15}$ in which n is 0-2; R^{15} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R^{11} and R^{15} are unsubstituted or are substituted with one or more
 25 substituents each selected independently from Z , which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{16}$, CO_2R^{16} , SH, $S(O)_nR^{16}$ in which n is 0-2, $NHOH$, $NR^{12}R^{16}$, NO_2 , N_3 , OR^{16} , $R^{12}NCOR^{16}$ and $CONR^{12}R^{16}$; R^{16} is hydrogen,
 30 alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R^{12} , which is selected independently from R^{11} and Z , is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{17}$ and $S(O)_nR^{17}$ in which n is 0-2; and R^{17} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy,
 35 cycloalkyl, cycloalkenyl or cycloalkynyl; each of R^{11} , R^{12} , R^{15} and R^{16} may be further substituted with the any of the groups set forth for Z , and R^{11} is preferably hydrogen, aryl, such as phenyl or alkyl phenyl, loweralkyl;

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or the compounds are 4-biphenylsulfonides in which Ar¹ is preferably N-(5-isoxazolyl) or N-(3-isoxazolyl).

Among the embodiments described in detail herein, Ar² is thienyl, furyl, pyrrolyl or a group that is a derivative or analog, as described below, of a thienyl, furyl or pyrrolyl group, including benzo[b] derivatives such as a benzo[b]thienyl, Ar¹ is N-(5-isoxazolyl) or N-(3-isoxazolyl). Ar² has the formula IV:



in which X is O, S or NR¹¹, where R¹¹ is as defined above;

that can be substituted at any or all positions or is an analog or derivative of the groups of formula (IV) in which the substituents form fused aromatic, aliphatic or heterocyclic rings; and R⁸, R⁹ and R¹⁰ are each independently selected as follows from (i) or (ii):

20 (i) R⁸, R⁹ and R¹⁰, which each contain hydrogen or up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, are each independently selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁸, (AcO)C=CHR¹⁸, CO₂R¹⁸, SH, (CH₂)_rC(O)(CH₂)_nR¹⁸,
 25 (CH₂)_r(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_rC(O)(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sC(O)(CH₂)_nR¹⁸, (CH₂)_rNH(CH=CH)_s(CH₂)_nR¹⁸, C=N(OH)(CH₂)_rR¹⁸, (CH₂)_r(CH=CH)_sNH(CH₂)_nR¹⁸, (CH₂)_rC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rR¹⁸, S(O)_mR¹⁸ in which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, HNOH, NR¹⁸R¹⁹, NO₂, N₃, OR¹⁸, R¹⁹NCOR¹⁸ and CONR¹⁹R¹⁸, in which R¹⁹ is selected from
 30 hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²⁰, S(O)_nR²⁰ in which n is 0-2; and R¹⁸ and R²⁰ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; and any of the groups set forth for R⁸, R⁹ and R¹⁰ are
 35 unsubstituted or substituted with any substituents set forth for Z; which is hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R²¹, CO₂R²¹, SH, S(O)_nR²¹ in which n is 0-2, NHOH, NR²²R²¹, NO₂, N₃, OR²¹, R²²NCOR²¹ and CONR²²R²¹; R²² is

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selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_nR^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl,

5 with the proviso that if R^8 is $NR^{18}R^{19}$, OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{18}R^{19}CO_2R^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$ or $(CH_2)_rR^{18}$ and R^{18} is an aryl group containing 5 or 6 members, then the aryl group has at least two substituents, and preferably one substituent at the 2-position relative to the linkage to the thienyl, furyl or

10 pyrrolyl;

(ii) any two of R^8 , R^9 and R^{10} with the carbon to which each is attached form an aryl, aromatic ring, heteroaromatic ring, carbocyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to 7 members that is substituted with one or

15 more substituents, each substituent is independently selected from Z; the other of R^8 , R^9 and R^{10} is selected as in (i); and the heteroatoms are NR^{11} , O, or S, with the proviso that Ar^2 is not 5-halo-3-loweralkylbenzo[b]thienyl, 5-halo-3-loweralkylbenzo[b]furyl, 5-halo-3-loweralkylbenzo[b]pyrrolyl.

In preferred embodiments of interest herein, R^9 and R^{10} are hydrogen, halide or

20 methyl, more preferably hydrogen or halide, and R^8 is selected from CO_2R^{18} , $(CH_2)_rC(O)(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $C=N(OH)(CH_2)_rR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, and $(CH_2)_rR^{18}$.

25 In certain embodiments, the compounds are selected with the proviso that if R^8 is CO_2R^{18} , $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$ or $(CH_2)_rR^{18}$ and R^{18} is phenyl, the phenyl group is substituted at at least two positions, and preferably, at least one of those positions is ortho.

In the preferred compounds, R^{18} is aryl or heteroaryl, preferably having 5 or 6

30 members in the ring, more preferably phenyl or pyrimidinyl, most preferably phenyl.

In the most preferred compounds herein, R^{18} is phenyl, which is substituted at more than one position, and most preferably at least one substituent is at the ortho position, R^9 and R^{10} are each hydrogen, halide or loweralkyl, preferably hydrogen, and R^8 is $C(O)NHR^{18}$, $C(O)CH_2R^{18}$, $(CH_2)_rR^{18}$, with the proviso that if R^8 is $C(O)NHR^{18}$, then the

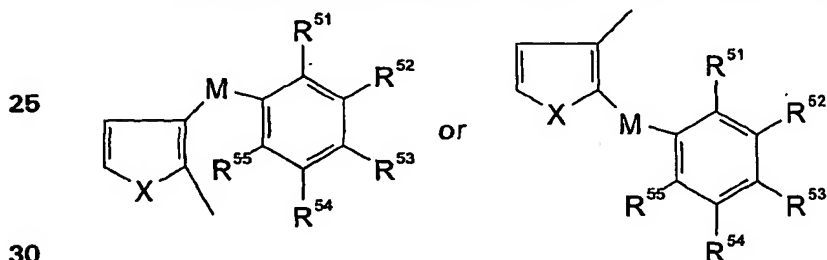
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phenyl group must have at least two substituents, preferably one of the substituents is in the ortho position.

In other preferred embodiments, Ar^2 is a benzo[b]thienyl, benzo[b]furyl, or indolyl (benzo[b]pyrrolyl), with the proviso that the benzene ring is substituted and the substituents are other than 5 halo, 3-loweralkyl. Preferred substituents on the benzene ring, include, but are not limited to, one or more selected from alkylenedioxy, particularly methylenedioxy, preferably 3,4-methylenedioxy, ethylenedioxy, aryl, particularly phenyl, dimethylamino, diethylamino, benzyl, alkoxy, particularly lower alkoxy, such as methoxy and ethoxy, halide, and alkyl, preferably loweralkyl.

- Preferred compounds also include compounds that are ET_B receptor selective or that bind to ET_B receptors with an IC_{50} of less than about $1 \mu M$. ET_B selective compounds interact with ET_B receptors at IC_{50} concentrations that are at least about 10-fold lower than the concentrations at which they interact with ET_A receptors. In these compounds, R^2 is selected from among alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, halide or H; and R^1 is halide or loweralkyl, and in preferred embodiments, R^1 is bromide or chloride, preferably chloride; R^9 and R^{10} are selected independently from hydrogen, loweralkyl, preferably methyl or ethyl, or halide, and R^8 , which is the substituent at the 5-position (see, e.g., formulae III and IV), is aryl or a heterocycle, particularly phenyl and isoxazolyl, which are unsubstituted or substituted with Z, which is preferably loweralkyl or halide.

Among the compounds of interest herein are those in which Ar^2 has the formula:



- in which M is $(CH_2)_mC(O)(CH_2)_r$, $(CH_2)_mC(O)NH(CH_2)_r$, $(CH_2)_m(CH=CH)(CH_2)_r$, $(CH_2)_mC(O)(CH_2)_sNH(CH_2)_r$, $(CH_2)_m(CH=CH)(CH_2)_r$, $C=N(OH)(CH_2)_r$, $(CH_2)_mC(O)(CH=CH)_sNH(CH_2)_r$, $CH(OH)(CH_2)_r$, $CH(CH_3)C(O)(CH_2)_r$, $CH(CH_3)C(O)(CH_2)_m(CH=CH)(CH_2)_r$, $(CH_2)_r$, $(CH_2)_rO$, $(CH_2)_rS(O)_n$ wherein n is 0-2, $C(O)O$, in which m, s and r are each independently 0 to 6, preferably 0 to 3, more preferably M is $(CH_2)_mC(O)(CH_2)_r$, $(CH_2)_mC(O)NH(CH_2)_r$, $(CH_2)_m(CH=CH)(CH_2)_r$,
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$(\text{CH}_2)_m\text{C}(\text{O})(\text{CH}_2)_5\text{NH}(\text{CH}_2)_r$, $(\text{CH}_2)_m(\text{CH}=\text{CH})(\text{CH}_2)_r$, $\text{C}=\text{N}(\text{OH})(\text{CH}_2)_r$, $\text{CH}(\text{OH})(\text{CH}_2)_r$, $(\text{CH}_2)_r$, $(\text{CH}_2)_r\text{O}$, $(\text{CH}_2)_r\text{S}(\text{O})_n$, $\text{C}(\text{O})\text{O}$;

R^{51} , R^{52} , R^{53} , R^{54} and R^{55} are each independently selected from

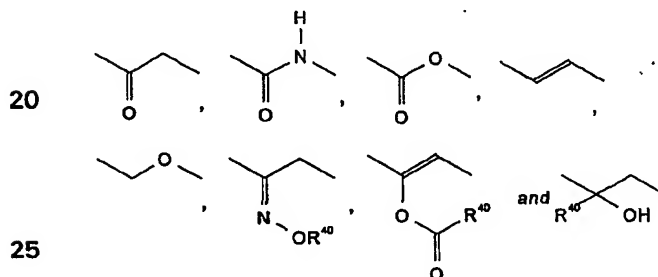
(i) or (ii) as follows:

- 5 (i) R^{51} , R^{52} , R^{53} , R^{54} and R^{55} are each independently selected from among H, OH, NHR^{38} , $\text{CONR}^{38}\text{R}^{39}$, NO_2 , cyano, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, haloalkyl, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, alkylcarbonyl, alkenylthio, alkenylamino, alkenyloxy, alkenyl sulfinyl, alkenylsulfonyl, alkoxycarbonyl, arylaminocarbonyl, alkylaminocarbonyl, aminocarbonyl, (alkyl-aminocarbonyl)alkyl, acetoxyl, hydroxyl, carboxyl, carboxyalkyl, carboxyalkenyl, alkylsulfonylaminoalkyl, cyanoalkyl, acetyl, acetoxylalkyl, hydroxylalkyl, alkoxyalkoxy, hydroxylalkyl, (acetoxyl)alkoxy, (hydroxyl)alkoxy, formyl, sulfonyl chlorides, amino acids, hexoses, O-glycosides, riboses, lower alkyl, CN, $-(\text{CH}_2)_x\text{C}(\text{O})(\text{CH}_2)_x$, $-(\text{CH}_2)_x$, $(\text{CH}_2)_x\text{N}$ -lower alkyl, $-(\text{CH}_2)_x\text{C}(\text{O})\text{NH}_2$, a D-, L- or racemic amino acid, a primary or secondary amide, O-glycoside, a hexose or ribose, $-\text{S}(\text{O})_2\text{NH}_2$, hydroxy, alkoxy, alkoxycarbonyl, acetoxylalkyl, $-(\text{CH}_2)_x\text{COOH}$; $-(\text{CH}_2)_x\text{COOH}-$, CO_2 -lower alkyl, CN, heteroaryl, $-\text{COC}(\text{O})(\text{CH}_2)_x\text{CH}_3$, $-(\text{CH}_2)_x\text{N}(\text{CH}_3)_2$, a sulfonyl chloride, $\text{S}(\text{O})_2\text{NHR}^{50}$, alkylaryl, alkylheteroaryl, $\text{C}(\text{O})\text{NHR}^{50}$, $-(\text{CH}_2)_x\text{OH}$, $-\text{C}(\text{O})\text{N}(\text{H})\text{N}(\text{H})\text{M}$, or;
- 10 (ii) at least two of R^{51} , R^{52} , R^{53} , R^{54} and R^{55} , which substitute adjacent carbons on the ring, together form alkylenedioxy, alkylenethioxyoxy or alkylenedithioxy (i.e. $-\text{O}-(\text{CH}_2)_n-\text{O}-$, $-\text{S}-(\text{CH}_2)_n-\text{O}-$, $-\text{S}-(\text{CH}_2)_n-\text{S}-$, where n is 1 to 4, preferably 1 or 2,) which is unsubstituted or substituted by replacing one or more hydrogens with halide, loweralkyl, loweralkoxy or halo loweralkyl, and the others of R^{51} , R^{52} , R^{53} , R^{54} and R^{55} are selected as in (i);
- 20 R^{38} and R^{39} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, haloalkyl alkylaryl, heterocycle, arylalkyl, arylalkoxy, alkoxy, aryloxy, cycloalkyl, cycloalkenyl and cycloalkynyl, and is preferably hydrogen, loweralkyl, loweralkoxy and lowerhaloalkyl;
- 25 X is S, O or NR^{11} , where R^{11} contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $\text{C}(\text{O})\text{R}^{15}$ and $\text{S}(\text{O})_n\text{R}^{15}$ in which n is 0-2; R^{15} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R^{11} and R^{15} are unsubstituted or are substituted with one or more substituents each selected
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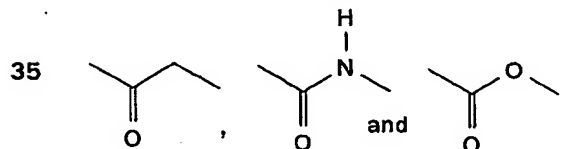
independently from Z, which as defined herein includes hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, amino acids, primary and secondary amides, O-glycosides, hexoses, riboses, alkylaryl, alkylheteroaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁶, OC(O)R¹⁶, CO₂R¹⁶, OCO₂R¹⁶,
 5 SH, S(O)_nR¹⁶ in which n is 0-2, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶; R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, chloride, NHR⁵⁰, alkylaryl, alkylheteroaryl, or -(CH₂)_xOH; R⁵⁰ is a substituent such as hydrogen, lower alkyl, or lower alkoxy; R¹², which is selected independently from R¹¹ and Z, is selected from
 10 hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2; R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹² and R¹⁶ may together form alkylene; each of R¹¹, R¹², R¹⁵ and R¹⁶ may be further substituted with the any of the appropriate groups of
 15 those set forth for Z.

X is preferably S, and M is preferably selected from among:



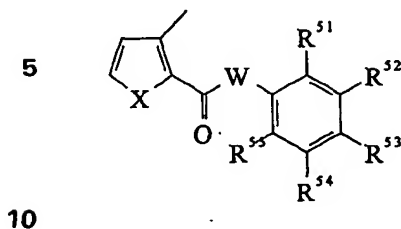
in which R⁴⁰ is preferably hydrogen, alkyl, alkoxy, alkoxyalkyl, haloalkyl, and more preferably loweralkyl, loweralkoxy, or halo loweralkyl, and is more preferably hydrogen
 30 or loweralkyl, particularly methyl or ethyl, and is most preferably hydrogen.

In more preferred compounds, M is C(O)CH₂, C(O)NH, -CH=CH-, CH₂CH₂C(O)(CH)₂, CH₂CHC(O)CH₂, and M is most preferably selected from among:



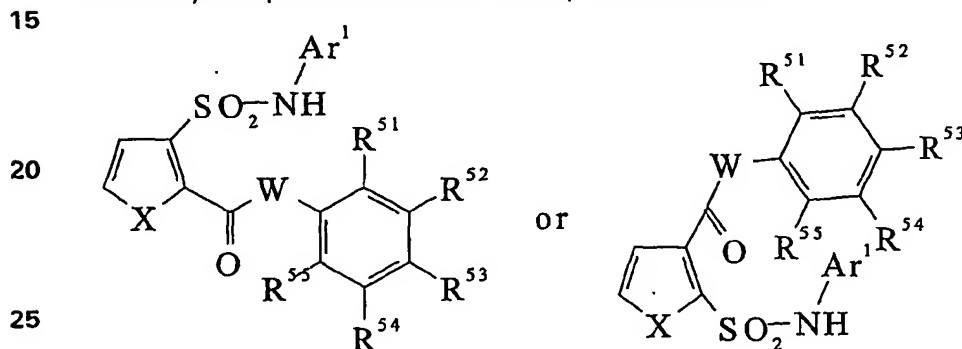
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Ar² most preferably has formula:



in which W is most preferably CH₂ or NH.

Thus, in this embodiment, the preferred sulfonamides or pharmaceutically or
veterinarily acceptable derivatives thereof, have the formula:



or pharmaceutically or veterinarily acceptable derivatives thereof, where Ar¹ is a
substituted or unsubstituted monocyclic or polycyclic, preferably a monocyclic or fused
30 bicyclic, aryl or heteroaryl group with one or more substituents, selected from, for
example, H, NH₂, halide, pseudohalide, alkyl, alkylcarbonyl, formyl, an aromatic or
heteroaromatic group, alkoxyalkyl, alkylamino, alkylthio, arylcarbonyl, aryloxy,
arylamino, arylthio, haloalkyl, haloaryl, carbonyl, in which the aryl and alkyl portions, are
unsubstituted or substituted with any of the preceding groups, and straight or
35 branched chains of from about 1 up to about 10-12 carbons, preferably, 1 to about 5 or
6 carbons. The substituents are preferably H, NH₂, halide, CH₃, CH₃O or another
aromatic group, and the sulfonamides are preferably the thiophene-3-sulfonamides. R⁵¹-
R⁵⁵ are as defined above.

In particular, Ar¹ is a five or six membered substituted or unsubstituted aromatic
40 or heteroaromatic ring or a fused bicyclic substituted or unsubstituted aromatic or
heteroaromatic ring, preferably an isoxazolyl, pyridazinyl, thiazolyl, pyrimidinyl or phenyl
groups and particularly 3- or 5-isoxazolyl, benzo-2,1,3-thiadiazol-5-yl, 2-pyrazinyl or
benzo-2,1,3-oxadiazol-5-yl;

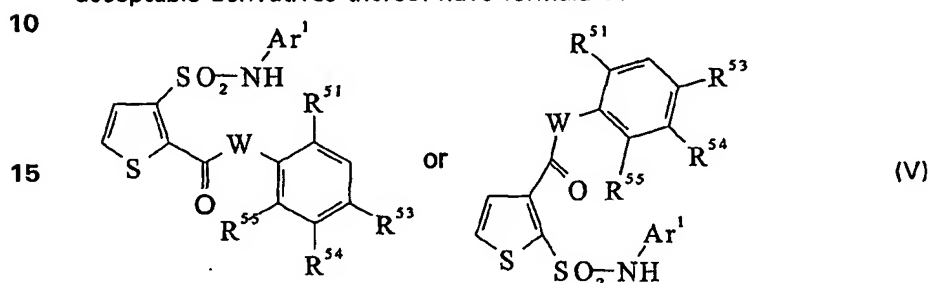
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W is $=C(\text{halo})_2$, $-(\text{CH}_2)_x-$, $=N(\text{lower alkyl})$, $-C(O)-$, $=C(\text{lower alkyl})_2$, $-\text{NH}-$, $=\text{NCOR}^{16}$, $-\text{NHC}(\text{R}^{12})(\text{R}^{16})-$, $=\text{NCO}_2\text{R}^{16}$ or $=\text{CHR}^{56}$; x is 0-3; R^{51} , R^{52} , R^{53} , R^{54} and R^{55} are each selected independently from Z, as defined above, or any two may form a ring containing two or more heteroatoms; and

- 5 R^{56} is H, or substituted or unsubstituted alkyl or aryl, preferably H or substituted or unsubstituted lower alkyl; more preferably H, methyl or carboxymethyl.

In all embodiments, X is preferably S.

In one embodiment, the sulfonamides and pharmaceutically or veterinarily acceptable derivatives thereof have formula V:



- 20 where Ar^1 , R^{51} and R^{53-55} are as defined above. In particular, Ar^2 is a five or six membered substituted or unsubstituted aromatic or heteroaromatic ring or a fused bicyclic substituted or unsubstituted aromatic or heteroaromatic ring, preferably 3- or 5-isoxazolyl, benzo-2,1,3-thiadiazol-5-yl, 2-pyrazinyl or benzo-2,1,3-oxadiazol-5-yl, more preferably 4-chloro-3-methyl-5-isoxazolyl or 4-chloro-5-methyl-3-isoxazolyl; W is $-\text{NH}-$, $=\text{NCOR}^{16}$, $=\text{NCO}_2\text{R}^{16}$, $-\text{NHC}(\text{R}^{12})(\text{R}^{16})-$ or is $-\text{CH}_2-$ when R^{54} is hydroxyl.
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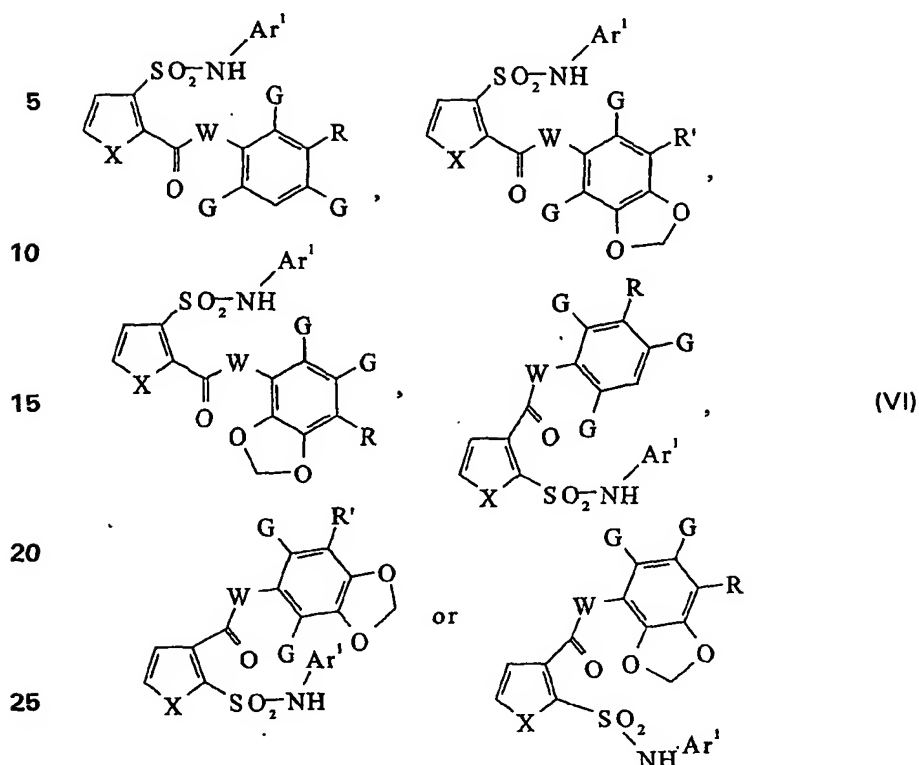
- 30 In preferred of these embodiments, R^{54} is selected from the group consisting of substituted and unsubstituted alkyl, hydroxyl, substituted and unsubstituted alkoxy, $\text{OC}(\text{O})\text{R}^{16}$, $\text{OCO}_2\text{R}^{16}$, $\text{NR}^{12}\text{R}^{16}$ and $\text{S}(\text{O})_n\text{R}^{16}$ in which n is 0-2, preferably alkoxycarbonylalkyl, carboxyalkyl, dialkylaminoalkyl, alkylsulfonylamino and aminosulfonyl.

In certain of these embodiments, when W is $-\text{NHC}(\text{R}^{12})(\text{R}^{16})-$, then R^{51} , R^{53} , R^{54} and R^{55} can be H.

- 35 R^{51} , R^{53} and R^{55} are preferably alkyl, haloalkyl, polyhaloalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, more preferably lower alkyl, lower alkenyl, lower alkynyl, or aryl, most preferably methyl. The sulfonamides are preferably thiophene-3-sulfonamides.

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In another embodiment, the sulfonamides have formulae VI:



where Ar¹ is as defined above. Ar¹ is a five or six membered substituted or
 30 unsubstituted aromatic or heteroaromatic ring or a fused bicyclic substituted or
 unsubstituted aromatic or heteroaromatic ring, preferably 3- or 5-isoxazolyl, benzo-
 2,1,3-thiadiazol-5-yl, 2-pyrazinyl or benzo-2,1,3-oxadiazol-5-yl;

X is preferably S;

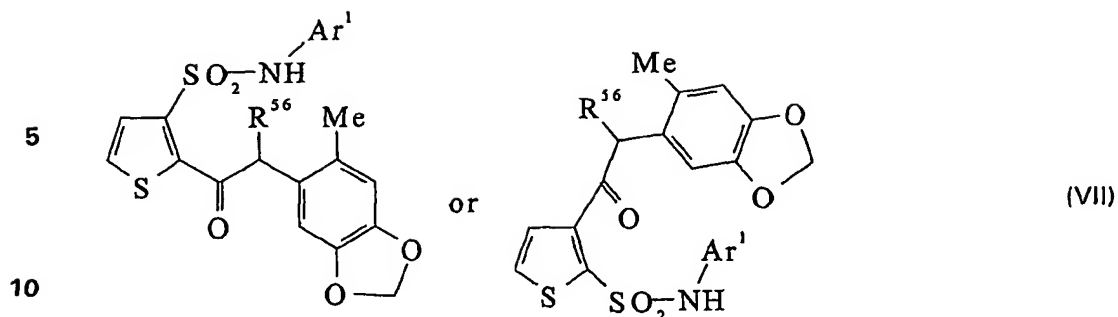
each G and R is independently selected from lower alkyl, CN,

35 $-(CH_2)_x C(O)(CH_2)_x$, $-(CH_2)_x$, $(CH_2)_x N$ -lower alkyl, $-(CH_2)_x C(O)NH_2$, a D-, L- or racemic
 amino acid, a primary or secondary amide, O-glycoside, a hexose or ribose, $-S(O)_2NH_2$,
 hydroxy, alkoxy, alkoxycarbonyl, acetoxymethyl, $-(CH_2)_x COOH$; $-(CH_2)_x COOH-$, CO_2-
 lower alkyl, CN, heteroaryl, $-COC(O)(CH_2)_x CH_3$, $-(CH_2)_x N(CH_3)_2$, a sulfonyl chloride,
 $S(O)_2NHR^{50}$, alkylaryl, alkylheteroaryl, $C(O)NHR^{50}$, $-(CH_2)_x OH$, $-C(O)N(H)N(H)M$; M is H
 40 or R⁵⁰; R' is selected from hydrogen, G and R; W is $=C(halo)_2$, $=N(H)$, $-(CH_2)_x-$,
 $=N(lower\ alkyl)$, $-C(O)-$, $=C(lower\ alkyl)_2$; and x is 0-3.

In another embodiment, the sulfonamides have formula VII:

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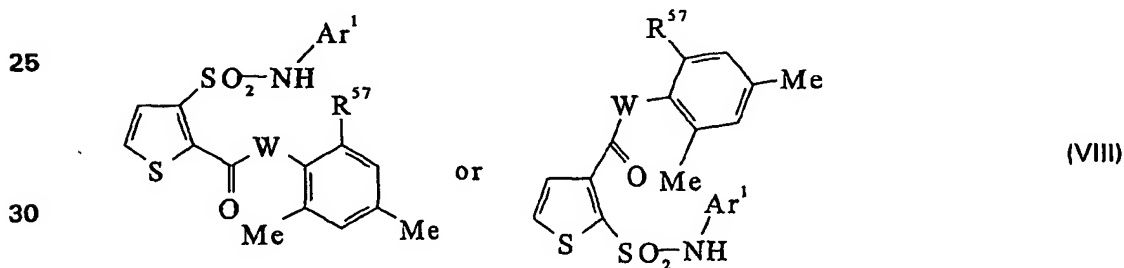


where:

Ar¹ is defined as above. Ar¹ is preferably benzo-2,1,3-oxadiazol-5-yl or 2-methoxy-3-pyrazinyl when R⁵⁶ is H; and R⁵⁶ is H, or substituted or unsubstituted alkyl or aryl, preferably H or substituted or unsubstituted lower alkyl, more preferably methyl or carboxymethyl.

In other embodiments of formula (IV), Ar¹ is preferably benzo-2,1,3-oxadiazol-5-yl or 2-methoxy-3-pyrazinyl when R⁵⁶ is H and R⁵⁶ is H, or substituted or unsubstituted alkyl or aryl, preferably H or substituted or unsubstituted lower alkyl, more preferably methyl or carboxymethyl.

In another embodiment, the sulfonamides have formula VIII:

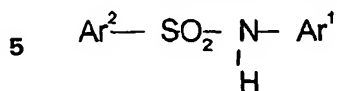


where Ar¹ is defined as above and is preferably 4-chloro-3-methyl-5-isoxazolyl; W is NH; and R⁵⁷ is selected from the group consisting of aryl, heteroaryl, heterocycle, OH, CN, C(O)R¹⁶, CO₂R¹⁶, SH, S(O)_nR¹⁶ in which n is 0-2, a D, L or racemic amino acid, a ribose or hexose, an O-glycoside, a sulfonyl chloride, -(CH₂)_xOH, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶; R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹² is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2; R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cyclo-

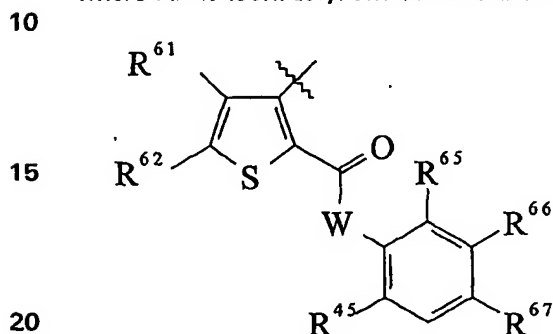
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alkyl, cycloalkenyl or cycloalkynyl; each of R^{12} , R^{15} and R^{16} may be further substituted with the any of the groups set forth for Z; R^{57} is preferably CONH^2 , COOH , or phenyl.

Preferred among the sulfonamide compounds are those of formula:



where Ar^1 is isoxazolyl and Ar^2 has the formula:



or a pharmaceutically or veterinarily acceptable derivative, including alkali metal salt, particularly sodium salt, thereof, wherein:

25 R^{61} and R^{62} are independently selected from the group consisting of hydrogen, halo, cyano, cyanoalkyl, $\text{C(O)}R^{41}$, alkyl, alkenyl, cycloalkyl and aryl, or together form alkylene;

W is O , NH or CH_2 ;

R^{65} , R^{66} and R^{67} are each independently selected as in (i) or (ii):

30 (i) R^{66} is hydrogen, unsubstituted alkyl, hydroxy, unsubstituted alkoxy, $\text{C(O)}R^{41}$, carbamoyloxy or alkoxycarbonyloxy, and

R^{65} and R^{67} are each independently selected from hydrogen, unsubstituted alkyl, hydroxy, $\text{C(O)}R^{41}$, carbamoyloxy and alkoxycarbonyloxy; or

(ii) if at least one of R^{61} and R^{62} is not hydrogen, then any two may form
35 alkylenedioxy, and the other is selected as in (i);

R^{45} is selected from the group consisting of alkyl, $\text{C(O)}R^{41}$, $(\text{CH}_2)_x\text{OH}$ and $\text{CH(OH)}(\text{CH}_2)_x\text{CH}_3$ in which x is 0-6, S(O)_nR^{41} in which n is 0-2 and $\text{C(=NR}^{43})R^{41}$;

R^{41} is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylsulfonylamino, arylsulfonylamino,
40 alkylsulfonylalkylamino, alkylsulfonylarylamine, arylsulfonylalkylamino or arylsulfonylarylamine; and

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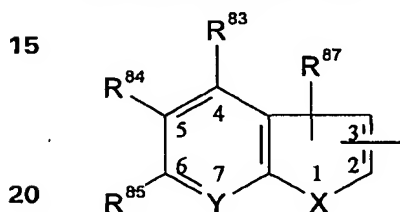
R^{43} is selected from hydroxy, alkoxy, alkyl and aryl, wherein

R^{41} and R^{43} are unsubstituted or substituted with one or more substituents selected from Y, which is alkoxy, halide, pseudohalide, carboxyl, alkoxy carbonyl, aryloxy carbonyl or hydroxy.

5 Thus, the sulfonamides of these embodiments are 2-acyl-3-thiophenesulfonamides. The corresponding 3-acyl-2-thiophenesulfonamides are also contemplated herein.

In other embodiments described in detail herein, Ar^2 is a fused ring bicyclic heterocycle and Ar^1 is preferably a five or 6-membered heterocyclic ring. Ar^1 is
10 preferably an isoxazole and Ar^2 is preferably a fused ring bicyclic heterocycle containing one heteroatom in each ring and containing 5 or 6 members in each ring.

In particular, Ar^2 is selected from among fused bicyclic heteroaryl groups, such as those having formula:



in which Y is N or O^+ , preferably N; X is S, O, NR^{11} , where R^{11} is as defined above;

R^{83} , R^{84} and R^{85} are selected from (i), (ii), (iii) or (iv):

25 (i) R^{83} , R^{84} and R^{85} are each selected independently from among H, $NHOH$, NH_2 , NO_2 , N_3 , halide, pseudohalide, alkyl, alkenyl, alkynyl, alkylaryl, aryloxy, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxy carbonyl, alkyl carbonyl, aryl carbonyl, formyl or amido, where the alkyl, alkenyl, alkynyl portions are straight or branched
30 chains of from about 1 up to about 10 carbons, preferably 1 to about 5 or 6 carbons and the aryl portions contain from 3 up to about 10 carbons, preferably 6 carbons; or, alternatively,

(ii) two of R^{83} , R^{84} and R^{85} together are substituted or unsubstituted 1,3-butadienyl, 4-dimethylamino-1,3 butadienyl, 1-chloro-1,3-butadienyl, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups or form alkylenedioxy; and the others of R^{83} ,
35 R^{84} and R^{85} are as defined in (i) above or also form substituted or unsubstituted 1,3-butadienyl, 4-dimethylamino-1,3 butadienyl, 1-chloro-1,3-butadienyl, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups or form alkylenedioxy; or alternatively,

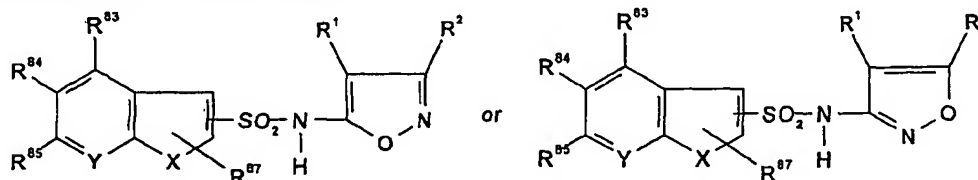
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(iii) two of R^{83} , R^{84} and R^{85} are independently selected from alkyl, alkoxy, halide, aminoalkyl, dialkylaminoalkyl, in which the alkyl and alkoxy groups contain from 1 to 10, preferably 1 to 6 carbons, and are straight or branched chains and the other is H; or

(iv) any two of R^{83} , R^{84} and R^{85} , which are each selected as in (i) form fused carbocyclic or heterocyclic rings; and

R^{87} is hydrogen or contains up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, and is selected hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, SH, $S(O)_n$, $(CH_2)_r R^{18}$, $C(O)R^{18}$, CO_2R^{18} , $(CH_2)_s COR^{18}$, OR^{18} , $(CH_2)_t CO(CH_2)_s R^{18}$, $S(O)_n R^{18}$ in which n is 0-2, and r and s are each independently 0 to 6, preferably 1-3, $HNOH$, $NR^{18}R^{19}$, NO_2 , N_3 , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}$, in which R^{19} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{20}$, $S(O)_n R^{20}$ in which n is 0-2; and R^{18} and R^{20} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; and any of the groups set forth for R^{87} is unsubstituted or substituted with any substituents set forth for Z, which is hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{21}$, CO_2R^{21} , SH, $S(O)_n R^{21}$ in which n is 0-2, $NHOH$, $NR^{22}R^{21}$, NO_2 , N_3 , OR^{21} , $R^{22}NCOR^{21}$ and $CONR^{22}R^{21}$; R^{22} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_n R^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl.

In more preferred embodiments Ar^1 is an isoxazole and the compounds are represented by the formulae IX:



in which Y is N or O^+ , preferably N; X is S, O, NR^{11} , in which R^{11} is as defined above, and is preferably hydrogen or aryl, more preferably hydrogen or phenyl; and

R^1 and R^2 are either (i), (ii) or (iii) as follows:

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(i) R^1 and R^2 are each independently selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, alkyloxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons; or,

(ii) R^1 and R^2 together form $-(CH_2)_n$, where n is 3 to 6; or,

10 (iii) R^1 and R^2 together form 1,3-butadienyl.

In preferred embodiments R^{87} is $(CH_2)_r R^{18}$, where R^{18} is aryl, preferably phenyl or pyrimidyl, more preferably phenyl, which is unsubstituted or substituted with alkyl, haloalkyl, halide, or such that two adjacent positions are substituted and together form alkylenedioxy, particularly methylenedioxy and ethylenedioxy.

15 In other preferred compounds R^{18} is $C(O)R^{27}$ in which R^{27} is aryl, and is preferably $(CH_2)_r C(O)(CH_2)_p$ -aryl, $(CH_2)_r C(O)$ aryl, $(CH_2)_r S(O)_q (CH_2)_p$ -aryl, $C(O)NR^{11}$ -aryl, $NHC(O)(CH_2)_r$ -aryl, NR^{11} -aryl, $(CH_2)_r$ aryl in which p and r are each independently selected from 0-10, preferably 0-6, more preferably 0-3, most preferably 0 or 1 and q is 0-3, preferably 0-2. The aryl portion is unsubstituted or is substituted with groups such as
20 alkyl, alkoxy, alkoxyalkyl, halogen, alkylenedioxy, particularly methylenedioxy, N-alkyl, N-alkoxy, amino, nitro and other such groups. The alkyl substituents are preferably lower alkyl, more preferably containing 1-3 carbons.

In the embodiments provided herein, the alkyl, alkynyl and alkenyl portions of each listed substituent are straight or branched chains, acyclic or cyclic, and preferably
25 have from about 1 up to about 10 carbons; in more preferred embodiments they have from 1-6 carbons. The aryl, alicyclic, aromatic rings and heterocyclic groups can have from 3 to 16, generally, 3-7, more often 5-7 members in the rings, and may be single or fused rings. The ring size and carbon chain length are selected up to an amount that the resulting molecule binds and retains activity as an endothelin antagonist or agonist,
30 such that the resulting compound inhibits binding by 50%, compared to binding in the absence of the sulfonamide, of an endothelin peptide to an endothelin receptor at a concentration of less than about 100 μM .

Of the compounds described herein, those that inhibit or increase an endothelin-mediated activity by about 50% at concentrations of less than about 10 μM are

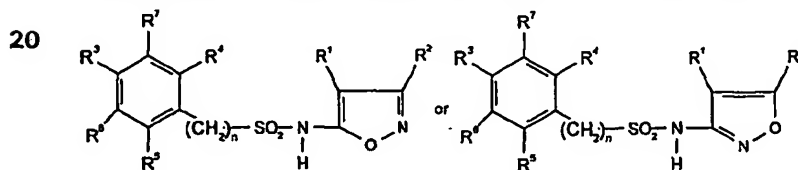
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preferred. More preferred are those that inhibit or increase an endothelin-mediated activity by about 50% at concentrations of less than about 1 μM , more preferably less than about 0.1 μM , even more preferably less than about 0.01 μM , and most preferably less than about 0.001 μM . It is noted that, as described below, the IC_{50} concentration
 5 determined in the *in vitro* assays is a non-linear function of incubation temperature. The preferred values recited herein refer to the assays that are performed at 4° C. When the assays are performed at 24° C, somewhat higher (see, the Tables) IC_{50} concentrations are observed. Accordingly, the preferred IC_{50} concentrations are about 10-fold higher.

The compounds of the preferred embodiments are described in further detail
 10 below.

1. Isoxazolylsulfonamides in which Ar^2 is phenyl, biphenyl and fused aromatic rings

Compounds in which Ar^2 is selected from phenyl, biphenyl, and aromatic fused rings, including naphthyl, anthracenyl, phenanthryl, indenyl, azulenyl, fluorenyl, and
 15 phenaziny. When Ar^2 is phenyl, biphenyl or naphthyl, the compounds are preferably (4-halo-isoxazolyl)sulfonamides or are (4-higher alkyl-isoxazolyl)sulfonamides, in which the alkyl group contains more than about 8, preferably 9 to 15, more preferably 9 to 13, carbon atoms. These compounds have the formulae (X):



in which n is 0 to 10, preferably 0 to 6, more preferably 0 to 3; R^3 , R^4 , R^5 , R^6 , and R^7 are selected from (i), (ii), (iii) or (iv) with the proviso that: (a) when Ar^2 is phenyl, at least one of R^3 , R^4 , R^5 , R^6 , and R^7 is not hydrogen, (b) when Ar^1 is 4-halo-5-methyl-3-
 30 isoxazolyl, R^3 is not NH_2 or CH_3 , and (c) when Ar^2 is phenyl, naphthyl or 2-biphenyl, R^1 is halide or higher alkyl:

(i) R^3 , R^4 , R^5 , R^6 , and R^7 are each selected independently from among H, NHOH , NH_2 , NO_2 , N_3 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio,
 35 arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, where the alkyl, alkenyl, alkynyl portions are straight or branched chains of from about 1 up to

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about 10 carbons, preferably, 1 to about 5 or 6 carbons and the aryl portions contain from 3 up to about 10 carbons, preferably 6 carbons; or, alternatively,

(ii) R^4 and R^7 together are substituted or unsubstituted 1, 3-butadienyl, 4-dimethylamino-1,3 butadiene, 1-chloro-1,3-butadiene, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R^3 , R^5 and R^6 are as defined in (i) above; or alternatively,

(iii) R^7 and R^3 together are substituted or unsubstituted 1, 3-butadienyl, 4-dimethylamino-1,3 butadiene, 1-chloro-1,3-butadiene, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and n , X , R^4 , R^5 and R^6 are as defined in (i) above; or

(iv) R^3 , R^5 , and R^7 are H are as defined in (i); and R^4 and R^6 are each independently selected from alkyl, alkoxy, halide aminoalkyl, dialkylaminoalkyl, in which the alkyl and alkoxy groups contain from 1 to 10, preferably 1 to 6 carbons, and are straight or branched chains.

In more preferred embodiments, R^2 is H, CH_3 , C_2H_5 ; R^1 is Cl, Br or CH_3 ; X is O or S; n is 0 or 1; and R^3 , R^4 , R^5 , R^6 , R^7 , are selected from either (i), (ii), (iii) or (iv) as follows:

(i) R^5 and R^6 are H; R^4 and R^7 are each independently selected from H, halide, NH_2 , CF_3 , Ph, CH_3 ; and R^3 is selected from H, $NHOH$, NH_2 , $EtNH_2$, $(CH_3)_2NH$, $Ph-CH_2NH$, NO_2 , F, Cl, Br, I, CN, CH_3 , $(CH_3)_3C$, C_5H_{11} , CH_3O , $n-C_4H_9O$, $CH_2=CH$, $Ph-CH=CH$, $CH\equiv C$, $Ph-CH\equiv C$, Ph, 3-(ethoxycarbonylmethyl)ureido, and 3-cyclohexylureido; or

(ii) R^4 and R^7 together form 1, 3-butadienyl, 4-chloro-1,3-butadienyl, 4-dimethylamino-1,3-butadienyl or 1-aza-1,3-butadienyl; and R^3 , R^5 and R^6 are defined as in (i) of this embodiment; or

(iii) R^7 and R^3 together form 1,3-butadienyl, 3-chloro-1,3-butadienyl 4-dimethylamino-1,3-butadienyl or 1-aza-1,3-butadienyl; and R^4 , R^5 and R^6 are as defined in (i) of this embodiment; or

(iv) R^3 , R^5 , and R^7 are H as defined in (i); and R^4 and R^6 are each independently selected from alkyl, alkoxy, halide, amino alkyl, alkylaminoalkyl or dialkylaminoalkyl, in which the alkyl and alkoxy groups contain from 1 to 10, preferably 1 to 6 carbons, and are straight or branched chains.

More preferred among the above compounds are those in which Ar^2 is a substituted or unsubstituted phenyl or naphthyl; R^1 is Br, Cl or I; R^2 is H, CH_3 , C_2H_5 , CF_3 , C_2F_5 , $n-C_3H_7$, $cycloC_3H_5$, and C_4H_9 ; and R^3 , R^4 , R^5 , R^6 and R^7 are either (i), (ii), (iii), (iv) or (v):

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(i) R^5 , R^6 and R^7 are H; n is 0 and R^3 is H, NH_2 , CH_3 , CF_3 , halide, C_2H_5NH or Ph, R^4 is H, CF_3 , NH_2 , R^7 is H or CF_3 , and R^5 and R^6 are H; or

(ii) R^3 , R^5 and R^6 are H; n is 0 and R^4 and R^7 together form 1,3-butadienyl, 4-dimethylamino-1,3 butadienyl, 1-chloro-1,3-butadiene, or 4-chloro-1,3-butadienyl; or

5 (iii) R^4 , R^5 and R^6 are H; n is 0; and R^7 and R^3 together form 1,3-butadienyl, 4-dimethylamino-1,3 butadienyl, 1-chloro-1,3-butadiene, 1-aza-1,3-butadienyl; or

(iv) R^4 is H or NH_2 , R^5 and R^6 are H; n is 1 and R^3 is H, NH_2 and halide; CH_3 , Br, Cl, F, CF_3 , NH_2 , R^7 is H, CH_3 , Br, Cl, F, NH_2 or CF_3 , and R^5 and R^6 are H; or

(v) R^3 , R^5 , and R^7 are H are as defined in (i); and R^4 and R^6 are each
10 independently selected from alkyl groups that contain from 1 to 6 carbons, and are straight or branched chains, lower alkoxy, and halide.

In more preferred embodiments, the benzenesulfonamides and naphthalenesulfonamides are N-(4-halo)-substituted N-isoxazolyisulfonamides or are 4-higher alkyl-substituted N-isoxazolyisulfonamides, in which R^2 is H, CH_3 , C_2H_5 , C_2F_5 or
15 CF_3 ; and R^3 , R^4 , R^5 , R^6 and R^7 are either (i) or (ii) as follows:

(i) R^4 , R^5 , R^6 and R^7 are each independently selected from H, halide, NH_2 , CF_3 , Ph and CH_3 ; R^3 is selected from H, $NHOH$, NH_2 , $C_2H_5NH_2$, $(CH_3)_2NH$, $Ph-CH_2NH$, NO_2 , F, Cl, Br, I, CN, CH_3 , $(CH_3)_3C$, C_6H_{11} , CH_3O , $n-C_4H_9O$, $CH_2=CH$, $Ph-CH=CH$, $CH\equiv C$, $Ph-CH\equiv C$, Ph, 3-(ethoxycarbonylmethyl)ureido, and 3-cyclohexylureido; or

20 (ii) R^3 , R^5 and R^7 are H; and R^4 and R^6 are each an alkyl group that contains from 1 to 3 carbons, which are straight or branched chains.

In yet more preferred embodiments, R^1 is most preferably Br; R^2 is CH_3 , C_2H_5 , or CF_3 ; and R^3 , R^4 , R^6 and R^7 are (i) or (ii) as follows:

(i) R^3 is H, NH_2 , CH_3 , CF_3 , halide or C_2H_5NH ; R^4 , R^5 and R^6 are independently
25 selected from H, CF_3 , halide, particularly Br and Cl, NH_2 ; and R^7 is H, CH_3 , CH_2CH_3 , $(CH_3)CH$, F or CF_3 ; or

(ii) R^3 , R^5 and R^7 and R^4 and R^6 are each a methyl or ethyl.

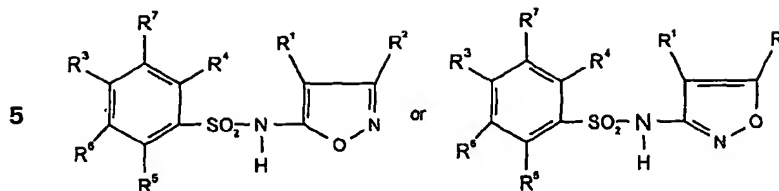
In all embodiments, R^1 is most preferably Br, except in instances in which enhanced ET_8 affinity, compared to the corresponding compound in which R_1 is CH_3 , is
30 desired, than R^1 is most preferably a higher alkyl (9 to 15 carbons, preferably 9 or 10 to 13 carbons).

a. Compounds in which Ar^2 is phenyl and biphenyl and n is 0

Compounds in which Ar^2 is phenyl or biphenyl have the following formulae (XI):

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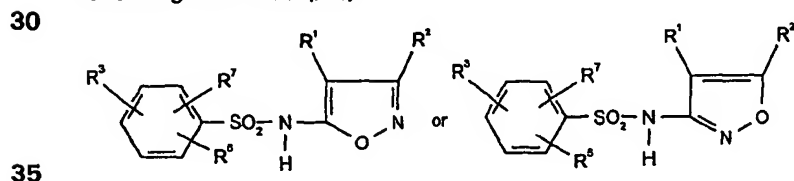


10 in which R^3 , R^4 , R^5 , R^6 , and R^7 are selected from (i), (ii), (iii) or (iv) with the proviso that, (a) when Ar^2 is phenyl, at least one of R^3 , R^4 , R^5 , R^6 , and R^7 is not hydrogen, (b) when Ar^2 is phenyl and Ar^1 is 3-isoxazolyl, R^3 is not NH_2 or CH_3 , and (c) when Ar^2 is naphthyl, 2-biphenyl, phenyl, other than benzofuryl, dibenzothienyl and dibenzopyrrolyl, R^1 is halide or higher alkyl:

15 (i) R^3 , R^4 , R^5 , R^6 , and R^7 are each selected independently from among H, NHOH, NH_2 , NO_2 , N_3 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, where
 20 the alkyl, alkenyl, alkynyl portions are straight or branched chains of from about 1 up to about 10 carbons, preferably, 1 to about 5 or 6 carbons and the aryl portions contain from 3 up to about 10 carbons, preferably 6 carbons; are each independently selected as described above; or, alternatively,

(ii) R^3 , R^5 , and R^7 are H; and R^4 and R^6 are each independently selected from
 25 alkyl, alkoxy, halide aminoalkyl, dialkylaminoalkyl, which are unsubstituted or substituted with alkyl groups, wherein the alkyl and alkoxy groups contain from 1 to 10, preferably 1 to 6 carbons, and are straight or branched chains.

Among the above phenyl and biphenyl compounds, are compounds with the following formulae (XII):



in which R^3 , R^5 and R^7 are each independently (a) hydrogen, except that at least one of R^3 , R^5 and R^7 is other than hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, or aralkoxy, any of
 40 which may be substituted with W^1 , W^2 and W^3 , except that if one of R^3 , R^5 or R^7 is

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alkyl at the 4 position, at least one of the other two of R^3 , R^5 and R^7 is not hydrogen; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro, except that if one of R^3 , R^5 and R^7 is 4-NO_2 , then at least one of the other two of R^3 , R^5 and R^7 is not hydrogen; (g) -C(O)H or -C(O)R^{27} ; (h) $\text{-CO}_2\text{H}$ or $\text{-CO}_2\text{R}^{27}$; (i) -SH , $\text{-S(O)}_n\text{R}^{27}$, $\text{-S(O)}_m\text{-OH}$, $\text{-S(O)}_m\text{-OR}^{27}$, $\text{-O-S(O)}_m\text{OH}$, or $\text{-O-S(O)}_m\text{OR}^{27}$; (j) $\text{-W}^4\text{NR}^{28}\text{R}^{29}$, except that, if one of R^3 , R^5 and R^7 is $4\text{-W}^4\text{NR}^{28}\text{R}^{29}$ then at least one of the other two of R^3 , R^5 and R^7 is not hydrogen; or (k) $\text{-W}^4\text{N(R}^{32}\text{)-W}^5\text{NR}^{30}\text{R}^{31}$;

R^1 and R^2 are selected from (i) or (ii) as follows:

- (i) R^1 is halide or is higher alkyl (greater than about 8 carbons up to about 9 carbons in the chain; R^2 is selected from: (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, or aralkoxy, any of which may be substituted with W^1 , W^2 and W^3 ; (c) hydroxyl; (d) cyano; (e) nitro; (f) -C(O)H or -C(O)R^{27} ; (g) $\text{-CO}_2\text{H}$ or $\text{-CO}_2\text{R}^{27}$; (h) -SH , $\text{-S(O)}_n\text{R}^{27}$, $\text{-S(O)}_m\text{-OH}$, $\text{-S(O)}_m\text{OR}^{27}$, $\text{-O-S(O)}_m\text{R}^{27}$, $\text{-O-S(O)}_m\text{OH}$, or $\text{-O-S(O)}_m\text{-OR}^{27}$; (i) $\text{-W}^4\text{-NR}^{28}\text{R}^{29}$; or (j) $\text{-W}^4\text{N(R}^{32}\text{)-W}^5\text{-NR}^{30}\text{R}^{31}$; or
- (ii) R^1 and R^2 are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, or aralkoxy, any of which may be substituted with W^1 , W^2 and W^3 ; (c) hydroxyl; (d) cyano; (e) nitro; (f) -C(O)H or -C(O)R^{27} ; (g) $\text{-CO}_2\text{H}$ or $\text{-CO}_2\text{R}^{27}$; (h) -SH , $\text{-S(O)}_n\text{R}^{27}$, $\text{-S(O)}_m\text{-OH}$, $\text{-S(O)}_m\text{OR}^{27}$, $\text{-O-S(O)}_m\text{R}^{27}$, $\text{-O-S(O)}_m\text{OH}$, or $\text{-O-S(O)}_m\text{-OR}^{27}$; (i) $\text{-W}^4\text{-NR}^{28}\text{R}^{29}$; (j) $\text{-W}^4\text{N(R}^{32}\text{)-W}^5\text{-NR}^{30}\text{R}^{31}$; or (k) halo;

R^{27} is alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

- R^{28} is (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ; (c) cyano; (d) hydroxyl; (e) -C(O)H or -C(O)R^{27} ; (f) $\text{-CO}_2\text{R}^{27}$; (g) -SH , $\text{-S(O)}_n\text{R}^{27}$, $\text{-S(O)}_m\text{-OH}$, $\text{-S(O)}_m\text{-OR}^{27}$, $\text{-O-S(O)}_m\text{R}^{27}$, $\text{-O-S(O)}_m\text{OH}$, or $\text{-O-S(O)}_m\text{-OR}^{27}$, except when W^4 is $\text{-S(O)}_n\text{-}$; R^{29} is (a) hydrogen; (b) -C(O)H or -C(O)R^{27} , except when W^4 is -C(O)- and R^{28} is -C(O)H , -C(O)R^{27} , or $\text{-CO}_2\text{R}^{27}$; (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ; or R^{28} and R^{29} together are alkylene or alkenylene (either of which may be substituted with W^1 , W^2 and W^3), completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached;

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R^{30} is (a) hydrogen; (b) hydroxyl; (c) $-C(O)H$ or $-C(O)R^{27}$; (d) $-CO_2R^{27}$; (e) $-SH$, $-S(O)_nR^{27}$, $-S(O)_m-OH$, $-S(O)_m-OR^{27}$, $-O-S(O)_m-R^{27}$, $-O-S(O)_m-OH$, or $-O-S(O)_m-OR^{27}$; (f) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

5 R^{31} is (a) hydrogen; (b) $-C(O)H$ or $-C(O)R^{27}$, except when W^6 is $-C(O)-$ and R^{30} is $-C(O)H$, $-C(O)R^{27}$, or $-CO_2R^{27}$; or (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

10 R^{32} is (a) hydrogen; (b) hydroxyl (c) $-C(O)H$, $-C(O)R^{27}$ or CO_2R^{27} ; or (d) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

or any two of R^{30} , R^{31} and R^{32} together are alkylene or alkenylene (either of which may be substituted with W^1 , W^2 and W^3), completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the atoms to which they are
15 attached;

W^1 , W^2 and W^3 are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkyl; (e) alkenyl; (f) aralkyl; (g) alkoxy; (h) aryloxy; (i) aralkoxy; (j) $-SH$, $-S(O)_nW^6$, $-S(O)_m-OH$, $-S(O)_m-OW^6$, $-O-S(O)_m-W^6$, $-O-S(O)_m-OH$, or $-O-S(O)_m-OW^6$; (k) oxo; (l) nitro; (m) cyano; (n) $-C(O)H$ or $-C(O)W^6$; (o) $-CO_2H$ or $-CO_2W^6$; (p) $-W^4-NW^7W^8$; (q) $W^4-N(W^{11})-W^5-W^6$; or (r) $-W^4-N(W^{11})-W^5-NW^7W^8$;

20 W^4 and W^5 are each independently (a) a single bond; (b) $-W^9-S(O)_n-W^{10}-$; (c) $-W^9-C(O)-W^{10}-$; (d) $-W^9-C(S)-W^{10}-$; (e) $-W^9-O-W^{10}-$; (f) $-W^9-S-W^{10}-$; or (g) $-W^9-O-C(O)-W^{10}-$;

W^6 , W^7 and W^8 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, or W^7 and W^8
25 together are alkylene or alkenylene, completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached; W^9 and W^{10} are each independently a single bond, alkylene, alkenylene, or alkynylene; W^{11} is (a) hydrogen; (b) hydroxyl; (c) $-C(O)H$, $-C(O)W^6$ or $-CO_2W^6$; (d) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl,
30 or aralkyl; or any two of W^7 and W^8 and W^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated, unsaturated, or aromatic ring together with the atoms to which they are attached; m is 1 or 2; and n is 0, 1, or 2.

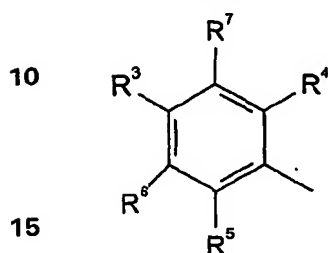
Preferred compounds include those in which one of R^3 , R^5 or R^7 is phenyl or phenoxy or compounds in which one of R^3 , R^5 or R^7 is hydrogen, one of the other two

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of R^3 , R^5 and R^7 is at the 2 position and is not hydrogen, and the other of R^3 , R^5 and R^7 is at the 5 position. Thus, preferred compounds are 2-substituted benzenesulfonamides, and 2,5-substituted benzenesulfonamides. In addition, in preferred compounds R^1 is preferably halide. Preferred substituents are lower alkyl, particular methyl, ethyl, and propyl, halide, amino, dimethylamino, and methoxy.

(1) Ar^2 is phenyl

In particular Ar^2 has the formula (XIII):



in which:

R^1 is halide or higher alkyl (greater than 8 carbons); R^2 selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, aminocarbonyl, haloalkyl, haloaryl, alkoxy carbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions are either straight or branched chains that contain from 1 up to about 10 carbon atoms, and the aryl portions contain from about 4 to about 14 carbons; and R^3 , R^4 , R^5 , R^6 , and R^7 are either (i) or (ii) as follows:

(i) R^3 , R^4 , R^5 , R^6 , and R^7 are selected independently from among H, $NHOH$, NH_2 , NO_2 , pseudohalide, including N_3 , halide, alkenyl, alkynyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxy carbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, where the alkyl, alkenyl, alkynyl portions are straight or branched chains of from about 1 up to about 10 carbons, preferably, 1 to about 5 or 6 carbons, are unsubstituted or substituted with groups, such as any set forth for R^8 , R^9 , R^{10} and R^{11} , above, and the aryl portions contain from 3 up to about 10 carbons, preferably 3 to 6 carbons, and, also are unsubstituted or substituted with groups, such as any set forth for R^8 , R^9 , R^{10} and R^{11} ; R^4 and R^6 are as defined in (i); or

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(i) R³ is H, NH₂, CH₃, CF₃, halide or C₂H₅NH; R⁴, R⁵ and R⁶ are independently selected from H, CH₃, C₂H₅, (CH₃)₂CH, CF₃, halide, particularly Br and Cl, NH₂; and R⁷ is H, CH₃, CH₂CH₃, (CH₃)CH, F or CF₃; or

(ii) R³, R⁵, and R⁷ are H; and R⁴ and R⁶ are each independently selected from
 5 alkyl groups in which the alkyl groups have from 1 to 3 carbons and may form straight or branched chains.

Of the above compounds those with ortho and/or meta substituents or those that are substituted at positions 2 and 5 on the benzene ring are generally more preferred, except when the resulting compound is a biphenyl and ET_B affinity is desired,
 10 then the corresponding para-substituted compounds are preferred. Compounds with ortho substituents are more generally more preferred than the corresponding meta-substituted compounds. This observation is particularly important when activity with respect to ET_A receptors is considered. In addition, in preferred compounds R¹ is preferably halide. Preferred substituents are lower alkyl, particular methyl, ethyl, and
 15 propyl, halide, amino, dimethylamino, and methoxy. Other preferred substituents may be deduced from the following Table.

Benzene sulfonamides were synthesized and tested using the exemplified assays (see, EXAMPLES) and selected results are set forth in Table 1 (the N-(3,4-dimethyl-5-isoxazoly)benzenesulfonamides are generally included for comparison with the
 20 corresponding N-(4-halo-3-methyl-5-isoxazoly)benzenesulfonamide.

TABLE 1

	COMPOUND	ET _A (μM)*	ET _B (μM)*
	N-(4-bromo-5-methyl-3-isoxazoly)benzenesulfonamide	0.097 ± 0.04	31 ± 5.3
25	N-(3-methyl-4-bromo-5-isoxazoly)benzenesulfonamide	0.055 ± 0.005	19.5 ± 4
	N-(4-chloro-3-methyl-5-isoxazoly)benzenesulfonamide	~0.11	25.6
30	4- <i>iso</i> -propyl-N-(4-bromo-3-methyl-5-isoxazoly)benzenesulfonamide	17.3	0.78
	4-bromo-N-(3,4-dimethyl-5-isoxazoly)benzenesulfonamide	8.9	14.4
	4-bromo-N-(4-bromo-3-methyl-5-isoxazoly)benzenesulfonamide	3.0	3.8

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(ii) R^3 , R^5 , and R^7 are H; and R^4 and R^6 are each independently selected from alkyl, alkoxy, halide, aminoalkyl, dialkylamino, dialkylaminoalkyl, which are unsubstituted or substituted with alkyl groups, and in which the alkyl and alkoxy groups contain from 1 to 10, preferably 1 to 6 carbons, and are straight or branched chains.

5 Compounds in which at least one of $R^3 - R^7$ is phenyl are discussed below with the biphenyl compounds.

In certain preferred embodiments: R^1 is halide or a higher alkyl selected from C_9H_{19} to $C_{13}H_{27}$; R^2 is selected independently from alkyl, lower alkenyl, lower alkynyl, lower haloalkyl and H; and R^3 , R^4 , R^5 , R^6 , and R^7 are either (i) or (ii) as follows:

10 (i) R^4 , R^5 , R^6 and R^7 are each independently selected from H, lower alkyl, NH_2 , NO_2 , halide, pseudohalide; R^3 is selected from H, $NHOH$, NH_2 , NO_2 , N_3 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, where the alkyl, alkenyl, alkynyl portions are straight or branched chains of from 1 up to 5 or 6 carbons and the aryl portions contain from 4 to 14 carbons; or

20 (ii) R^3 , R^5 , and R^7 are H; and R^4 and R^6 are each independently selected from alkyl, alkoxy, halide, aminoalkyl, and dialkylaminoalkyl, which are unsubstituted or substituted with alkyl groups, and in which the alkyl and alkoxy groups contain 1 to 6 carbons, and are straight or branched chains.

25 In more preferred embodiments, R^1 is Cl or Br, or if greater ET_B activity is preferred a higher alkyl (C_9H_{19} to $C_{13}H_{27}$); R^2 is selected from H, CH_3 , C_2H_5 , CF_3 , C_2F_5 , $n-C_3H_7$, cyclo- C_3H_7 , $nC_{13}H_{27}$ and nC_9H_{19} ; and R^3 , R^4 , R^5 , R^6 , and R^7 are either (i) or (ii) as follows:

30 (i) R^4 , R^5 , R^6 and R^7 are each independently selected from H, halide, NH_2 , CF_3 , Ph and CH_3 ; R^3 is selected from H, $NHOH$, NH_2 , $C_2H_5NH_2$, $(CH_3)_2NH$, $Ph-CH_2NH$, NO_2 , F, Cl, Br, I, CN, CH_3 , $(CH_3)_3C$, C_5H_{11} , CH_3O , $n-C_4H_9O$, $CH_2=CH$, $Ph-CH=CH$, $CH\equiv C$, $Ph-CH\equiv C$, Ph, 3-(ethoxycarbonylmethyl)ureido, and 3-cyclohexylureido; or

(ii) R^3 , R^5 , and R^7 are H; and R^4 and R^6 are each independently selected from alkyl and aminoalkyl in which the alkyl groups have from 1 to 6 carbons that may from straight or branched chains.

In yet more preferred embodiments, R^1 is Br, Cl or C_9H_{19} to $C_{13}H_{27}$; R^2 is H, CH_3 , C_2H_5 , or CF_3 ; and R^3 , R^4 , R^5 , R^6 , and R^7 are either (i) or (ii) as follows:

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	4-fluoro-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	7 ± 3	57 ± 13
	4-fluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	1.2	15.3
5	3-nitro-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	13.7	--
	3-nitro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	2.8	40
10	4-iodo-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	6.3 ± 2.5	1.05 ± 0.08
	4-chloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	1.96 ± 1	7.02 ± 2
	N-(4-bromo-3-ethyl-5-isoxazolyl)benzenesulfonamide	0.47 ± 0.3	67.1 ± 6
15	4-methyl-N-(4-bromo-3-methyl-5-isoxazolyl)-4-benzenesulfonamide	1.44 ± 0.8	4.0 ± 0.9
	2,5-dimethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.044 ± 0.03	15.5 ± 3
20	2-fluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.20	40.8
	3-fluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.21	38.3
	2,5-dimethyl-N-(3,4-di-methyl-5-isoxazolyl)benzenesulfonamide	9.4	66.3
25	2,5-dimethyl-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	0.19	30.7
	4-acetamido-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	18.1	--
30	4-acetamido-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	6.4 ± 3.5	~ 26
	4-nitro-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	100	10
	4-nitro-N-(4-bromo-5-methyl-3-isoxazolyl)benzenesulfonamide	53 ± 1.0	9.4 ± 2
35	2,4,6-trimethyl-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	52 ± 4	—

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	2,4,6-trimethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	5.9 ± 0.9	45.5 ± 4.4
	4-iodo-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	36 ± 3	6
5	4-iodo-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	6.3 ± 2.5	1.05 ± 0.08
	4-chloro-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	10.2 ± 1.5	29.2 ± 0.07
10	4-chloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	1.96 ± 1	7.02 ± 2
	2-chloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	.071 ± .06	37 ± 2
	3,4-dichloro-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	3.8 ± 1.5	25 ± 6
15	3,4-dichloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	**0.90 ± 0.2 0.48 ± 0.07	6.9 ± 1.8 6.5 ± 0.9
	2,4-dichloro-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	14 ± 7	104 ± 12
20	2,4-dichloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	2.6 ± 0.3	24 ± 7
	2-fluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.16 ± 0.04	35 ± 6
	3-fluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.14 ± 0.06	24.8
25	2,5-dimethyl-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	12.7 ± 6.7	12
	4-nitro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	19 ± 5	6.8 ± 3
30	4-butoxy-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	9.2	7.4
	4-butoxy-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	3.0 ± 0.7	2.0 ± 0.8
	3-chloro-2-methyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.165 ± 0.13	22 ± 15
35	2-methyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.12 ± 0.01	13 ± 1

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	3-chloro-2,5-dimethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.31 ± 0.03	11.2 ± 0.3
	2,6-difluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.16 ± 0.1	63 ± 10
5	2,5-difluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	2.4 ± 0.2	26.8 ± 3.7
	2,3,4-trichloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	2.1 ± 0.01	10.2 ± 2.0
10	2,3-dichloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.19 ± 0.04	20.4 ± 2.3
	2,5-dichloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.113 ± 0.02	25 ± 3
	5-bromo-2-methoxy-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.072 ± 0.03	5.3 ± 0.4
15	2-bromo-5-ethyl-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	0.057	3.5 ± 0.4
	2-bromo-5-methyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.046 ± 0.002	11.5 ± 4
20	2-bromo-5-ethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.029 ± 0.010	5.2 ± 1.1
	5-bromo-2-ethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.0028 ± 0.002	5.2 ± 1.1
	2,5-diethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.0062 ± 0.003	5.2 ± 0.8
25	2,5-diethyl-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	0.027 ± 0.01	17 ± 7
	2-bromo-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.040 ± 0.02	39 ± 4
30	2-cyano-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.18 ± 0.02	~80
	2,4,5-trichloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	1.2 ± 0.1	23 ± 3
	3,4-dimethoxy-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.49 ± 0.18	24 ± 5
35	4-trifluoromethyl-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	129	12.1

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	COMPOUND	ET _A (μM) [*]	ET _B (μM) [*]
	4-trifluormethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	22 ± 3.0	3.0 ± 0.2
	3-trifluoromethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	1.5 ± 0.2	21 ± 0.4
5	2,5-dimethoxy-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.19 ± 0.03	14 ± 0.7
	5-chloro-2-methoxy-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.94 ± 0.14	10.2 ± 1
10	3-chloro-2-methyl-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	10.2 ± 1.5	29.2 ± 0.7
	3-chloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.23 ± 0.06	34.7 ± 1.4
	N-(4-bromo-3-trifluoromethyl-5-isoxazolyl)benzenesulfonamide	0.33 ± 0.08	34.7 ± 1.4
15	N-(4-isothiocyanato-3-methyl-5-isoxazolyl)benzenesulfonamide	0.62 ± 0.3	—
	3-carboxyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.18 ± 0.05	7.6 ± 2.7
20	3,5-dichloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.062 ± 0.02	14.2 ± 1.0
	3-chloro-5-fluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.54 ± 0.1	17.0 ± 0.7
	3,5-di(trifluoromethyl)-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.57 ± 0.07	17.1 ± 0.6
25	2,5-difluoro-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	0.19 ± 0.05	58 ± 10
	2-chloro-5-methyl-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	0.22 ± 0.04	49 ± 2
30	2,5-dichloro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.58 ± 0.25	17.4 ± 0.8
	2-chloro-4-fluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	~ 2.0	31 ± 0.3
	2,5-difluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.16 ± 0.1	63 ± 10
35	2-chloro-5-methyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	1.26 ± 0.19	37 ± 1

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	2-methyl-5-amino-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.34 ± 0.01	~ 100
	2-methyl-5-dimethylamino-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.21 ± 0.03	44 ± 8
5	3-acetamido-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.35 ± 0.05	4.0 ± 1
	3-bromo-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.23 ± 0.06	9.4 ± 1.4
10	2-phenoxy-5-nitro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.79 ± 0.14	19.5 ± 0.1
	4-ethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.34 ± 0.05	083 ± 0.05
	2,5-dibromo-3,6-difluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.035	13.3 ± 1
15	2-trifluoromethoxy-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.017	55 ± 7
	2-methyl-5-fluoro-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.099	78 ± 8
20	2-butyl-5-bromo-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.038	3.6 ± 0.3
	2-bromo-5-butyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.85 ± 0.11	5.4 ± 0.3
	2-methyl-5-bromo-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.24	13 ± 2
25	2,5-dipropyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.19 ± 0.3	14.4 ± 1.8
	2-dimethylamino-5-methyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	8.1 ± 0.2	0.93 ± 0.25
30	2-methylamino-5-methyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.0081 ± 0.0002	0.93 ± 0.25
	2-methylamino-5-methyl-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	0.0032 ± 0.0001	5.6 ± 0.6
	2-methyl-5-dimethylamino-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.25 ± 0.01	31 ± 4
35	2-ethyl-5-dimethylamino-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.16	23

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	2-methyl-5-azido-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.28 ± 0.04	4.2 ± 0.1
	2,4-diethyl-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	0.62 ± 0.13	11.5 ± 3.4
5	2,4-diethyl-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	0.56 ± 0.08	9.3 ± 3
	2-butyl-5-bromo-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	0.051	4.4 ± 0.1
10	2-bromo-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	0.086	--
	2-bromo-5-butyl-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	1.1	4.6 ± 0.6
	2-propyl-5-bromo-N-(3,4-dimethyl-5-isoxazolyl)	~.020	26 ± 4
15	2-propyl-5-bromo-N-(4-bromo-3-methyl-5-isoxazolyl)benzenesulfonamide	~0.006	6.55 ± 0.2
	2-propyl-5-bromo-N-(4-chloro-3-methyl-5-isoxazolyl)benzenesulfonamide	—	14 ± 4
	4-(N'-Cyclohexylureido-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide	3.8 ± 0.3	100 ± 5
20	N-(4-nonyl-3-trifluoromethyl-5-isoxazolyl)benzenesulfonamide	8.7 ± 0.5	9.2 ± 0.7
	N-(4-tridecyl-3-trifluoromethyl-5-isoxazolyl)benzenesulfonamide	13.2 ± 2	1.8 ± 0.5
25	N-(4-ethyl-3-trifluoromethyl-5-isoxazolyl)benzenesulfonamide	0.12 ± 0.02	27 ± 3
	N-(4-hexyl-3-trifluoromethyl-5-isoxazolyl)benzenesulfonamide	11 ± 2.0	63 ± 9

* results generally from 1, 2 or 3 experiments with the same preparation

30 ** Two preparations

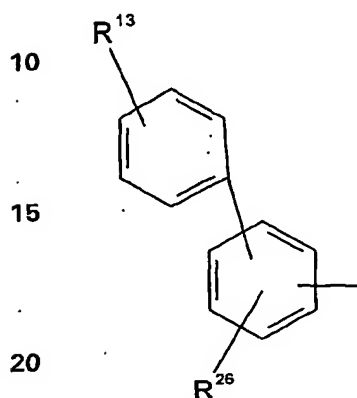
(2) Ar² is biphenyl

In certain of the embodiments herein, Ar¹ is N-(5-isoxazolyl) or N-(3-isoxazolyl) with R¹ and R² selected as described above, and Ar² is a substituted benzene group in which one of R³, R⁴, R⁵, R⁶ and R⁷ is selected independently from phenyl or substituted phenyl. The remaining of R³, R⁴, R⁵, R⁶ and R⁷ are selected as described in (1) above for
 35 embodiments in which Ar² is phenyl. R¹ and R² are also selected as described in (1)

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above, except in instances when one of R^3 , R^4 , R^5 , R^6 and R^7 is at the 3 or 4 position so that the resulting compounds are 3- or 4-biphenyl compounds. In these instances, R^2 is selected as described above, but R^1 can be halide and higher alkyl, and in addition, can be any of the substituents set forth for R^2 . For the 3- or 4-biphenyl compounds R^1 is preferably halide, lower alkyl, particularly CH_3 , or C_6H_{19} - $C_{13}H_{27}$.

In certain embodiments, Ar^2 is unsubstituted or substituted biphenyl group of formula (XIV):



in which each ring may have one or more substituents each selected independently from R^{26} and R^{13} where:

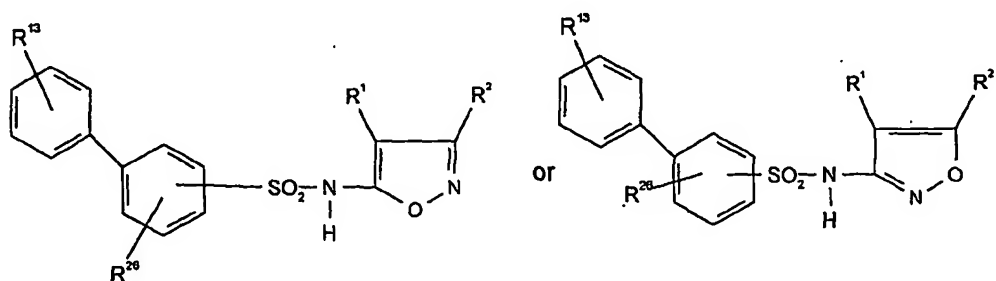
- (i) R^{26} and R^{13} are independently selected from H, OH, OHNH, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, dialkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, carbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms, preferably from 1 to 6 atoms, and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons, preferably 4 to 10 carbons; or
- (ii) R^{26} and R^{13} together (see, Formula IVb) are $-CH_2-$, $-CH=CH-$, O, S, NR^{11} in which R^{11} is as defined above, and is preferably, H or alkyl, particularly lower alkyl. It is understood that in either (i) or (ii) each ring of Ar^2 may be unsubstituted or substituted with more than one substituent, each of which is selected independently from the selections set forth in (i) for R^{26} and R^{13} .

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These compounds, thus, include biphenylsulfonamides, fused tricyclic-substituted sulfonamides dibenzothiophenesulfonamides, dibenzofuransulfonamides, dibenzopyrrolefonamides (carbazolesulfonamides) and phenanthrenesulfonamides. The

5 dibenzothiophenesulfonamides, dibenzofuransulfonamides, dibenzopyrrolefonamides and phenanthrenesulfonamides are discussed separately with the compounds in which Ar² is a heterocycle with one heteroatom and two or more fused rings.

Among preferred embodiments herein, Ar² is has formula (XV):



in which R²⁶ and R¹³ are each independently selected from H, OH, OHNH, NH₂, NO₂, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy,

10 alkylamino, dialkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, carbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms, preferably from 1 to 6

15 atoms, and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons, preferably 4 to 10 carbons. R¹³ and R²⁶ are preferably each selected from from H, loweralkyl, haloalkyl and halide. Again, it is understood that Ar² may be substituted with more than one substituent, each of which is selected independently from the selections set forth for R²⁶ and R¹³, and R² and R¹ are

20 as defined above.

Again, it is understood that Ar² may be substituted with more than one substituent, each of which is selected independently from the selections set forth for R²⁶ and R¹³.

In preferred embodiments, in which the sulfonamides are biphenylsulfonamides

25 in which R¹ is halide; R² is selected from alkyl, lower alkenyl, lower alkynyl, lower haloalkyl and H; and R²⁶ and R¹³ are selected from H, lower alkyl, haloalkyl and halide. In preferred of these embodiments, R¹ is Cl or Br, and for the 3-biphenylsulfonamides

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and 4-biphenylsulfonamides, R¹ is also CH₃; R² is selected from H, CH₃, C₂H₅, CF₃, C₂F₅, n-C₃H₇ and cyclo-C₃H₇; and R²⁶ and R¹³ are each independently selected from H, halide, NH₂, CF₃, CH₃, CN, CH₃, (CH₃)₃C, C₆H₁₁, CH₃O, n-C₄H₉O and CH₂=CH.

In yet more preferred embodiments, R² is H, CH₃, C₂H₅, or CF₃; R²⁶ and R¹³ are
 5 independently selected from H, CH₃, C₂H₅, CF₃, and halide.

In another preferred embodiment, the biphenylsulfonamides are 3- or 4-biphenylsulfonamides, in such instances R¹ is preferably, halide or methyl. Such compounds have a higher ET_B affinity than the 2-biphenylsulfonamides. It is also preferred that the substituent at the 2-position is hydrogen. R¹ is selected from halide,
 10 CH₃, C₂H₅, CF₃, C₂F₅, n-C₃H₇ and cyclo-C₃H₇, preferably halide or CH₃, and R² is selected from H, CH₃, C₂H₅, CF₃, C₂F₅, n-C₃H₇ and cyclo-C₃H₇; and R²⁶ and R¹³ are each independently selected from H, halide, NH₂, CF₃, CH₃, CN, CH₃, (CH₃)₃C, C₆H₁₁, CH₃O, n-C₄H₉O and CH₂=CH. In more preferred of these embodiments, R¹ is halide or CH₃, and R² are selected from H, CH₃, C₂H₅, or CF₃; R²⁶ and R¹³ are independently selected from
 15 H, CH₃, C₂H₅, CF₃, and halide.

In certain embodiments herein, the biphenylsulfonamides are substituted 4-biphenylsulfonamides, R¹³ is preferably at the para position and R²⁶, if it is not hydrogen, is at any position except the 2-position.

In more preferred embodiments, R¹ is halide or methyl or higher (C₉-C₁₃) alkyl.
 20 R¹ is selected from halide, CH₃, C₂H₅, CF₃, C₂F₅, n-C₃H₇ and cyclo-C₃H₇, preferably halide or CH₃, and R² is selected from H, CH₃, C₂H₅, CF₃, C₂F₅, n-C₃H₇ and cyclo-C₃H₇, more preferably R¹ is halide or CH₃, and R² is selected from H, CH₃, C₂H₅, or CF₃.

In more preferred embodiments, R¹ is Cl or Br, or if greater ET_B activity is preferred a higher alkyl (C₉H₁₉ to C₁₃H₂₇); R² is selected from H, CH₃, C₂H₅, CF₃, C₂F₅, n-C₃H₇, cyclo-C₃H₇, nC₁₃H₂₇ and nC₉H₁₉. In yet more preferred embodiments, R¹ is Br, Cl
 25 or C₉H₁₉ to C₁₃H₂₇; R² is H, CH₃, C₂H₅, or CF₃.

The biphenyl compounds provided herein are generally ET_B active or ET_B selective (see, e.g., Table 2); i.e., the compounds provided herein inhibit binding of endothelin to ET_B receptors at concentrations about 10- to about 30-fold less than they
 30 inhibit binding of endothelin to ET_A receptors. In particular the 4-biphenylsulfonamides are ET_B selective.

Exemplary biphenyl sulfonamides are the following and those set forth in Table 2, and include, but are not limited to:

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N-(3-methyl-5-isoxazolyl)-4'-methylphenyl-4-biphenylsulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-4'-methylphenyl-4-biphenylsulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-4'-methylphenyl-4-biphenylsulfonamide, (3-methyl-5-isoxazolyl)-4'-trifluorophenyl-4-biphenylsulfonamide, (4-bromo-3-methyl-5-isoxazolyl)-4'-trifluorophenyl-4-biphenylsulfonamide, (3-methyl-5-isoxazolyl)-4'-methoxyphenyl-4-biphenylsulfonamide, (4-bromo-3-methyl-5-isoxazolyl)-4'-methoxyphenyl-4-biphenylsulfonamide, (4-bromo-3-methyl-5-isoxazolyl)-3'-methoxyphenyl-4-biphenylsulfonamide, (4-bromo-3-methyl-5-isoxazolyl)-2'-methoxyphenyl-4-biphenylsulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-3',4'-methylenedioxyphenyl-4-biphenylsulfonamide and (4-bromo-3-methyl-5-isoxazolyl)-3'-methylphenyl-4-biphenylsulfonamide. Corresponding 4-chloro and 4-fluoro isoxazolyl compounds are also encompassed herein.

Exemplary biphenyl compounds were tested using the exemplified assays (see, EXAMPLES) and the results, which are intended to be exemplary or provided for comparison with compounds provided herein, and are not limiting, are as set forth in the following table (Table 2):

TABLE 2

	COMPOUND	ET _A (μM)*	ET _B (μM)*
	N-(4-bromo-3-methyl-5-isoxazolyl)-4-biphenylsulfonamide	3.3 49 [†]	~0.17 1.23 [†]
20	N-(4-bromo-5-methyl-3-isoxazolyl)-4-biphenylsulfonamide	6.4 ± 2 49 [†]	0.29 ± 0.02 1.78 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-4-biphenylsulfonamide	4.93 ± 3	0.29 ± 0.1
25	N-(3,4-dimethyl-5-isoxazolyl)-4-biphenylsulfonamide	9.9 ± 1.4 6.3 [†]	0.77 ± 0.32 0.15 [†]
	N-(4-chloro-5-methyl-3-isoxazolyl)-4-biphenylsulfonamide	3.7 18.6 [†]	0.23 ± 0.01 1.29 [†]
	N-(4-Methyl-3-trifluoromethyl-5-isoxazolyl)-4-biphenylsulfonamide	19.0 --	1.7 5.62 [†]
30	N-(4-Tridecyl-3-trifluoromethyl-5-isoxazolyl)-4-biphenylsulfonamide	34.0 ± 9 33.0 [†]	0.99 ± 0.2 0.95 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-biphenylsulfonamide	0.0083 ± 0.0014	12.8
35	N-(4-bromo-3-methyl-5-isoxazolyl)-2-biphenylsulfonamide	0.00127**	8.54**

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-biphenylsulfonamide	0.00123**	~14**
	N-(3,4-dimethyl-5-isoxazolyl)-3-biphenylsulfonamide	>0.03**	3.48**
5	N-(4-bromo-3-methyl-5-isoxazolyl)-3-biphenylsulfonamide	>0.03**	0.76**
	N-(4-chloro-3-methyl-5-isoxazolyl)-3-biphenylsulfonamide	>0.03**	0.793**
10	N-(4-bromo-3-methyl-5-isoxazolyl)-4'-methylphenyl-4-biphenylsulfonamide	14.53 ± 9.6 22.17 ± 3.77 [†]	0.046 ± 0.044 0.168 ± 0.0032 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-4'-trifluorophenyl-4-biphenylsulfonamide	5.4 ± 0.3 25.9 ± 13.7 [†]	0.083 ± 0.02 0.71 ± 0.43 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-4'-methoxyphenyl-4-biphenylsulfonamide	14.7 ± 5.6 121.5 ± 2.12 [†]	1.15 ± 0.44 3.94 ± 0.89 [†]
15	N-(4-bromo-3-methyl-5-isoxazolyl)-3'-methoxyphenyl-4-biphenylsulfonamide	4.97 ± 3.4 162.6 ± 7.14 [†]	0.66 ± 0.25 2.08 ± 0.23 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2'-methoxyphenyl-4-biphenylsulfonamide	3.3 ± 3.5	0.41 ± 0.14
20	N-(4-bromo-3-methyl-5-isoxazolyl)-3',4'-methylenedioxyphenyl-4-biphenylsulfonamide	38.2 ± 4.95 [†]	3.0 ± 0.78 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3'-methylphenyl-4-biphenylsulfonamide	—	—

* results generally from 1, 2 or 3 experiments with the same preparation

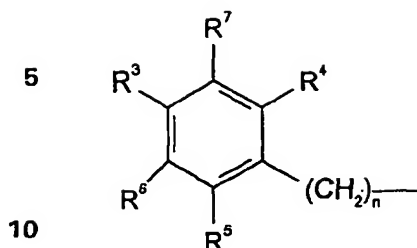
25 ** preliminary results

Preferred compounds are those in which Ar² is a 4-biphenyl in which, referring to formula VII and at least one substituent R¹³ is at the para position. Preferred substituents are loweralkyl, halo loweralkyl and lower alkoxy. Such compounds are ET_B active.

30 b. Compounds in which Ar² is phenyl and biphenyl and n > 0Ar² has formula (XVI):

35

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These compounds include those in which n is 1 to 10, preferably 1 to 6, more preferably 1 to 3; R¹ and R² are either (i), (ii) or (iii) as follows:

15 (i) R¹ and R² are each independently selected from H, NH₂, NO₂, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, aminocarbonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or
20 unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions are either straight or branched chains that contain from 1 up to about 10 carbon atoms, and the aryl portions contain from about 4 to about 14 carbons, except the R² is not halide or pseudohalide; or,

(ii) R¹ and R² together form -(CH₂)_n, where n is 3 to 6; or,

25 (iii) R¹ and R² together form 1,3-butadienyl; and

R³, R⁴, R⁵, R⁶, and R⁷ are selected from (i), (ii), (iii) or (iv):

(i) R³, R⁴, R⁵, R⁶, and R⁷ are each selected independently from among H, NHOH, NH₂, NO₂, N₃, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio,
30 arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, where the alkyl, alkenyl, alkynyl portions are straight or branched chains of from about 1 up to about 10 carbons, preferably, 1 to about 5 or 6 carbons and the aryl portions contain from 3 up to about 10 carbons, preferably 6 carbons; or, alternatively,

35 (ii) R⁴ and R⁷ together are substituted or unsubstituted 1, 3-butadienyl, 4-dimethylamino-1,3 butadiene, 1-chloro-1,3-butadiene, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R³, R⁵ and R⁶ are as defined in (i) above; or alternatively,

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(iii) R⁷ and R³ together are substituted or unsubstituted 1, 3-butadienyl, 4-dimethylamino-1,3 butadiene, 1-chloro-1,3-butadiene, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R⁴, R⁵ and R⁶ are as defined in (i) above; or

(iv) R³, R⁵, and R⁷ are H are as defined in (i); and R⁴ and R⁶ are each
 5 independently selected from alkyl, alkoxy, halide aminoalkyl, dialkylaminoalkyl, which are unsubstituted or substituted with alkyl groups, in which the alkyl and alkoxy groups contain from 1 to 10, preferably 1 to 6 carbons, and are straight or branched chains.

In more preferred embodiments, R² is H, CH₃, C₂H₅, CF₃, C₂F₅, n-C₃H₇, cyclo-C₃H₇ and C₄H₉; R¹ is Br, Cl, CH₃, or, if greater ET_B affinity is desired, is higher alkyl; n is
 10 1-3; and R³, R⁴, R⁵, R⁶, R⁷, are selected from either (i), (ii), (iii) or (iv) as follows:

(i) R⁵ and R⁶ are H; R⁴ and R⁷ are each independently selected from H, halide, NH₂, CF₃, Ph, CH₃; and R³ is selected from H, NHOH, NH₂, EtNH₂, (CH₃)₂NH, Ph-CH₂NH, NO₂, F, Cl, Br, I, CN, CH₃, (CH₃)₃C, C₆H₁₁, CH₃O, n-C₄H₉O, CH₂=CH, Ph-CH=CH, CH≡C, Ph-CH≡C, Ph, 3-(ethoxycarbonylmethyl)ureido, and 3-cyclohexylureido; or

15 (ii) R⁴ and R⁷ together form 1, 3-butadienyl, 4-chloro-1,3-butadienyl, 4-dimethylamino-1,3-butadienyl or 1-aza-1,3-butadienyl; and R³, R⁵ and R⁶ are defined as in (i) of this embodiment; or

(iii) R⁷ and R³ together form 1,3-butadienyl, 3-chloro-1,3-butadienyl 4-dimethylamino-1,3-butadienyl or 1-aza-1,3-butadienyl; and R⁴, R⁵ and R⁶ are as defined
 20 in (i) of this embodiment; or

(iv) R³, R⁵, and R⁷ are H as defined in (i); and R⁴ and R⁶ are each independently selected from alkyl, alkoxy, halide, amino alkyl, alkylaminoalkyl or dialkylaminoalkyl, which are unsubstituted or substituted with alkyl groups, in which the alkyl and alkoxy groups contain from 1 to 10, preferably 1 to 6 carbons, and are straight or branched
 25 chains.

More preferred among the above compounds are those in which n is 1 to 3; R¹ is Br, Cl, I or CH₃ or, if greater ET_B affinity is desired, is C₉H₁₉-C₁₃H₂₇; R² is H, CH₃, C₂H₅, CF₃, C₂F₅, n-C₃H₇, cyclo-C₃H₇ and C₄H₉; either R³, R⁴, R⁵, R⁶ and R⁷ are either (i), (ii), (iii), (iv) or (v):

30 (i) R⁵, R⁶ and R⁷ are H; and R³ is H, NH₂, CH₃ CF₃, halide, C₂H₅NH or Ph, R⁴ is H, CF₃, NH₂, R⁷ is H or CF₃, and R⁵ and R⁶ are H; or

(ii) R³, R⁵ and R⁶ are H; and R⁴ and R⁷ together form 1,3-butadienyl, 4-dimethylamino-1,3 butadienyl, 1-chloro-1,3-butadiene, or 4-chloro-1,3-butadienyl; or

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(iii) R^4 , R^5 and R^6 are H; and R^7 and R^3 together form 1,3-butadienyl, 4-dimethylamino-1,3 butadienyl, 1-chloro-1,3-butadiene, 1-aza-1,3-butadienyl; or

(iv) R^4 is H or NH_2 , R^5 and R^6 are H; and R^3 is H, NH_2 and halide; CH_3 , Br, Cl, F, CF_3 , NH_2 , R^7 is H, CH_3 , Br, Cl, F, NH_2 or CF_3 , and R^5 and R^6 are H; or

- 5 (v) R^3 , R^5 , and R^7 are H are as defined in (i); and R^4 and R^6 are each independently selected from alkyl groups that contain from 1 to 6 carbons, and are straight or branched chains.

- In more preferred embodiments, the compounds are N-(4-halo-isoxazoly)-sulfonamides in which R^2 is H, CH_3 , C_2H_5 , C_2F_5 or CF_3 ; and R^3 , R^4 , R^5 , R^6 and R^7 are
10 either (i) or (ii) as follows:

(i) R^4 , R^5 , R^6 and R^7 are each independently selected from H, halide, NH_2 , CF_3 , Ph and CH_3 ; R^3 is selected from H, $NHOH$, NH_2 , $C_2H_5NH_2$, $(CH_3)_2NH$, $Ph-CH_2NH$, NO_2 , F, Cl, Br, I, CN, CH_3 , $(CH_3)_3C$, C_5H_{11} , CH_3O , $n-C_4H_9O$, $CH_2=CH$, $Ph-CH=CH$, $CH\equiv C$, $Ph-C\equiv C$, Ph, 3-(ethoxycarbonylmethyl)ureido, and 3-cyclohexylureido; or

- 15 (ii) R^3 , R^5 and R^7 are H; and R^4 and R^6 are each an alkyl group that contains from 1 to 3 carbons, which are straight or branched chains.

In yet more preferred embodiments, n is 1; R^1 is most preferably Br, Cl or CH_3 ; R^2 is CH_3 , C_2H_5 , or CF_3 ; and R^3 , R^4 , R^6 and R^7 are (i) or (ii) as follows:

- (i) R^3 is H, NH_2 , CH_3 , CF_3 , halide or C_2H_5NH ; R^4 , R^6 and R^6 are independently
20 selected from H, CF_3 , halide, particularly Br and Cl, NH_2 ; and R^7 is H, CH_3 , CH_2CH_3 , $(CH_3)CH$, F or CF_3 ; or

(ii) R^3 , R^5 and R^7 and R^4 and R^6 are independently selected from nitro, hydrogen, methyl or ethyl.

The following selected compounds are among the above compounds:

25

TABLE 3

COMPOUND	ET_A (μM)	ET_B (μM)
N-(3,4-Dimethyl-5-isoxazolyl)- α -toluenesulfonamide	7.5 ± 0.2	84.3 ± 9
2-nitro-N-(3,4-dimethyl-5-isoxazolyl)- α -toluenesulfonamide	23.8	--

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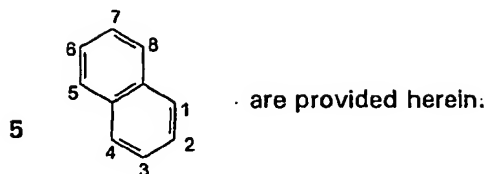
c. Compounds in which Ar^2 is a fused aromatic ring

Compounds in which Ar^2 contains fused aromatic rings and is selected from naphthyl, anthracenyl and phenanthryl are provided herein.

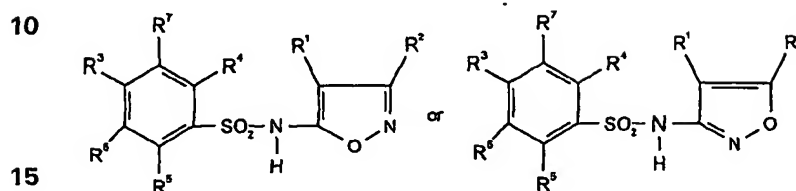
(1) Ar^2 is naphthyl

- 35 Compounds in which Ar^2 is naphthyl

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The compounds have formulae (XI):



in which R¹ and R² are as set forth above, R² is preferably H, lower alkyl or lower haloalkyl; R¹ is preferably halide or, if an increase in ET_B affinity is desired, higher alkyl (about 8 to 15, preferably 9 to 13 carbons, which are straight or branched chains); R³, R⁴, R⁵, R⁶, and R⁷ are selected from (i) or (ii):

(i) R⁴ and R⁷ together are substituted or unsubstituted 1, 3-butadienyl, 4-dimethylamino-1,3 butadiene, 1-chloro-1,3-butadiene, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R³, R⁵ and R⁶ are each selected independently from among H, NHOH, NH₂, NO₂, N₃, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, where the alkyl, alkenyl, alkynyl portions are straight or branched chains of from about 1 up to about 10 carbons, preferably, 1 to about 5 or 6 carbons and the aryl portions contain from 3 up to about 10 carbons, preferably 6 carbons; or alternatively,

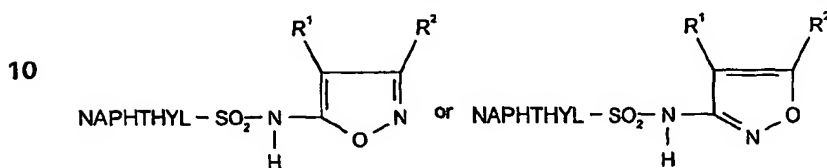
(ii) R⁷ and R³ together are substituted or unsubstituted 1, 3-butadienyl, 4-dimethylamino-1,3 butadiene, 1-chloro-1,3-butadiene, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R⁴, R⁵ and R⁶ are each selected independently from among H, NHOH, NH₂, NO₂, N₃, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkylalkoxy, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, where the alkyl, alkenyl, alkynyl portions are straight or branched chains of from

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about 1 up to about 10 carbons, preferably, 1 to about 5 or 6 carbons and the aryl portions contain from 3 up to about 10 carbons, preferably 6 carbons.

In preferred embodiments R^2 is H, CH_3 , C_2H_5 or CF_3 and R^1 is halide or, in embodiments in which an increase in ET_B activity is desired, R^1 is higher alkyl, in which the alkyl group contains between 8 and 15, preferably 9 and 13, carbons, which may be straight or branched chains.

In certain embodiments the compounds have formulae (XVII):



- 15 which is substituted with R^4 , R^5 and R^6 which are selected independently: (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) $-\text{C}(\text{O})\text{H}$ or $-\text{C}(\text{O})\text{R}^{27}$; (h) $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^{27}$; (i) $-\text{SH}$, $-\text{S}(\text{O})_n\text{R}^{27}$, $-\text{S}(\text{O})_m\text{OH}$, $-\text{S}(\text{O})_m\text{OR}^{27}$, $-\text{O}-\text{S}(\text{O})_m\text{R}^{27}$, $-\text{O}-\text{S}(\text{O})_m\text{OH}$, or $-\text{O}-\text{S}(\text{O})_m\text{OR}^{27}$; (j) $-\text{W}^4\text{-NR}^{28}\text{R}^{29}$, or (k) $-\text{W}^4\text{-N}(\text{R}^{32})\text{-W}^5\text{-NR}^{30}\text{R}^{31}$;
- 20

R^1 and R^2 are selected from (i) or (ii) as follows:

- (i) R^1 is halide or higher alkyl (greater than 8 carbons up to about 15); R^2 is (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ; (c) hydroxyl; (d) cyano; (e) nitro; (f) $-\text{C}(\text{O})\text{H}$ or $-\text{C}(\text{O})\text{R}^{27}$; (g) $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^{27}$; (h) $-\text{SH}$, $-\text{S}(\text{O})_n\text{R}^{27}$, $-\text{S}(\text{O})_m\text{OH}$, $-\text{S}(\text{O})_m\text{OR}^{27}$, $-\text{O}-\text{S}(\text{O})_m\text{R}^{27}$, $-\text{O}-\text{S}(\text{O})_m\text{OH}$, or $-\text{O}-\text{S}(\text{O})_m\text{OR}^{27}$; (i) $-\text{W}^4\text{-NR}^{28}\text{R}^{29}$; or (j) $-\text{W}^4\text{-N}(\text{R}^{32})\text{-W}^6\text{-NR}^{30}\text{R}^{31}$; or
- 25
- (ii) R^1 and R^2 are each independently selected from (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ; (c) hydroxyl; (d) cyano; (e) nitro; (f) $-\text{C}(\text{O})\text{H}$ or $-\text{C}(\text{O})\text{R}^{27}$; (g) $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^{27}$; (h) $-\text{SH}$, $-\text{S}(\text{O})_n\text{R}^{27}$, $-\text{S}(\text{O})_m\text{OH}$, $-\text{S}(\text{O})_m\text{OR}^{27}$, $-\text{O}-\text{S}(\text{O})_m\text{R}^{27}$, $-\text{O}-\text{S}(\text{O})_m\text{OH}$, or $-\text{O}-\text{S}(\text{O})_m\text{OR}^{27}$; (i) $-\text{W}^4\text{-NR}^{28}\text{R}^{29}$; (j) $-\text{W}^4\text{-N}(\text{R}^{32})\text{-W}^6\text{-NR}^{30}\text{R}^{31}$; or (k) halo;
- 30

R^{27} is alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ,

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R^{28} is (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with

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W^1 , W^2 and W^3 ; (c) cyano; (d) hydroxyl; (e) $-C(O)H$ or $-C(O)R^{27}$; (f) $-CO_2H$ or $-CO_2R^{27}$; (g) $-SH$, $-S(O)_nR^{27}$, $-S(O)_m-OH$, $-S(O)_m-OR^{27}$, $-O-S(O)_m-R^{27}$, $-O-S(O)_mOH$, or $-O-S(O)_m-OR^{27}$, except when W^4 is $-S(O)_n-$;

- R^{29} is (a) hydrogen; (b) $-C(O)H$ or $-C(O)R^{27}$, except when W^4 is $-C(O)-$ and R^{28} is -
- 5 $C(O)H$, $-C(O)R^{27}$, $-CO_2H$, or $-CO_2R^{27}$; (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 , or

- R^{28} and R^{29} together are alkylene or alkenylene (either of which may be substituted with W^1 , W^2 and W^3), completing 3- to 8-membered saturated, unsaturated
- 10 or aromatic ring together with the nitrogen atom to which they are attached;

- R^{30} is (a) hydrogen; (b) hydroxyl; (c) $-C(O)H$ or $-C(O)R^{27}$; (d) $-CO_2H$ or $-CO_2R^{27}$; (e) $-SH$, $-S(O)_nR^{27}$, $-S(O)_m-OH$, $-S(O)_m-OR^{27}$, $-O-S(O)_m-R^{27}$, $-O-S(O)_mOH$, or $-O-S(O)_m-OR^{27}$; (f) alkyl, alkynyl, alkenyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

- 15 R^{31} is (a) hydrogen; (b) $-C(O)H$ or $-C(O)R^{27}$, except when W^8 is $-C(O)-$ and R^{30} is $-C(O)H$, $-C(O)R^{27}$, $-CO_2H$, or $-CO_2R^{27}$; (c) alkyl, alkenyl, alkenyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

- R^{32} is (a) hydrogen; (b) hydroxyl, CO_2R^{27} or CO_2H , except when one of R^{30} and
- 20 R^{31} is hydroxyl, CO_2R^{27} or CO_2H ; (c) $-C(O)H$ or $-C(O)R^{27}$; or (d) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

- or any two of R^{30} , R^{31} and R^{32} together are alkylene or alkenylene (either of which may be substituted with W^1 , W^2 and W^3), completing a 3- to 8-membered
- 25 saturated, unsaturated or aromatic ring together with the atoms to which they are attached;

- W^1 , W^2 and W^3 are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkoxy; (e) $-SH$, $-S(O)_nW^6$, $-S(O)_m-OH$, $-S(O)_m-OW^6$, $-O-S(O)_m-W^6$, $-O-S(O)_mOH$, or $-O-S(O)_m-OW^6$; (f) oxo; (g) nitro; (h) cyano; (i) $-C(O)H$ or $-C(O)W^6$; (j) $-CO_2H$ or $-CO_2W^6$; or
- 30 (k) $-NW^7W^8$, $-C(O)NW^7W^8$, or $-S(O)_nW^7W^8$;

W^4 and W^5 are each independently (a) a single bond; (b) $-S(O)_n-$; (c) $-C(O)-$; (d) $-C(S)-$; or (e) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

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W⁶, W⁷ and W⁸ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, or W⁷ and W⁸ together are alkylene or alkenylene, completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are
 5 attached; m is 1 or 2; and n is 0, 1, or 2.

In certain embodiments, at least one of R⁴, R⁵ and R⁶ is not hydrogen. In other embodiments, at least one of R⁴, R⁵ and R⁶ is preferably di-loweralkylamino or loweralkylamino and the others of R⁴, R⁵ and R⁶ is hydrogen or lower alkyl.

In all preferred embodiments the sulfonamide is linked at position 1 or 2,
 10 preferably 1, of the naphthyl group and at least one of the substituents is at position 5.

Naphthalenesulfonamides were synthesized and tested using the exemplified assays (see, EXAMPLES) and selected results are set forth in the Table 4 (the 4-haloisoxazole compounds are preferred).

TABLE 4

15	COMPOUND	ET _A (μM)*	ET _B (μM)*
	N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide	0.44 ± 0.05	49 ± 9
	6-chloro-N-(3,4-dimethyl-5-isoxazolyl)-2-naphthalenesulfonamide	3.4 ± 0.3	7.8 ± 0.4
20	5-chloro-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide	2.4 ± 1	20 ± 5
	N-(4-bromo-3-methyl-5-isoxazolyl)-1-naphthalenesulfonamide	0.086	14.9 ± 5
25	N-(4-bromo-5-methyl-3-isoxazolyl)-1-naphthalenesulfonamide	0.1	16
	N-(4-methyl-3-trifluoromethyl-5-isoxazolyl)-1-naphthalenesulfonamide	0.64	62
	N-(4-ethyl-3-trifluoromethyl-5-isoxazolyl)-1-naphthalenesulfonamide	0.26	40
30	N-(4-bromo-3-ethyl-5-isoxazolyl)-1-naphthalenesulfonamide	0.97	41
	N-(4-bromo-3-methyl-5-isoxazolyl)-1-naphthalenesulfonamide	0.11	16
35	5-dimethylamino-N-(3,4-dimethyl-isoxazolyl)-1-naphthalenesulfonamide	0.0064	14

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COMPOUND	ET _A (μM)*	ET _B (μM)*
5-dimethylamino-N-(4-bromo-3-methyl-5-isoxazolyl)-1-naphthalenesulfonamide	0.0012	3.07
5-dimethylamino-N-(4-bromo-5-methyl-3-isoxazolyl)-1-naphthalenesulfonamide	0.002	2.5

5 * results generally from 1 to 4 experiments

(2) phenanthryl and anthracenyl

Isloxazolyl-sulfonamides in which Ar² contains three fused aromatic rings are also provided herein. R¹ and R² are selected as described above for the compounds in which Ar² is phenyl or biphenyl and n > 0. The fused rings may be substituted with one or
 10 more substituents selected from R¹³ and R²⁶ in which R²⁶ and R¹³ are independently selected from H, OH, OHNH, NH₂, NO₂, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, dialkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxy carbonyl, carbonyl, alkyl carbonyl, aminocarbonyl, aryl carbonyl,
 15 formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms, preferably from 1 to 6 atoms, and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons, preferably 4 to 10 carbons.

20 More preferably R¹ is halide or methyl; R² is selected from alkyl, lower alkenyl, lower alkynyl, and lower haloalkyl; and R²⁶ and R¹³ are selected from H, lower alkyl, haloalkyl and halide. In more preferred embodiments, R¹ is Cl, Br or CH₃; R² is selected from H, CH₃, C₂H₅, CF₃, n-C₃H₇, cyclo-C₃H₇ and C₄H₉; and R²⁶ and R¹³ are each independently selected from H, halide, NH₂, CF₃, CH₃, CN, CH₃, (CH₃)₃C, C₅H₁₁, CH₃O, n-
 25 C₄H₉O and CH₂=CH. In yet more preferred embodiments, R² is H, CH₃, C₂H₅, or CF₃; R²⁶ and R¹³ are independently selected from H, CH₃, C₂H₅, CF₃, and halide.

Exemplary compounds include N-(4-bromo-3-methyl-5-isoxazolyl)phenanthrene-3-sulfonamide, N-(4-bromo-5-methyl-3-isoxazolyl)phenanthrene-3-sulfonamide and N-(3,4-dimethyl-5-isoxazolyl)phenanthrene-3-sulfonamide. Selected results for such
 30 compounds are set forth in Table 5:

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TABLE 5

5	COMPOUND	ET _A (μM)*	ET _B (μM)*
	N-(4-bromo-3-methyl-5-isoxazolyl)-9,10-dioxoanthracene-2-sulfonamide	4.34	2.01
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-phenanthrenesulfonamidesulfonamide	~1.9	~0.06
	N-(3,4-dimethyl-5-isoxazolyl)-2-phenanthrenesulfonamidesulfonamide	~3.4	0.23

10 * preliminary results

2. Compounds in which Ar² is contains a heterocyclic ring or fused rings with at least one heterocyclic ring

Compounds in which Ar² is a heterocycle including sulfonamides in which Ar² is five-membered heterocyclic ring compound with one heteroatom and fused ring analogs thereof, compounds in which Ar² is a five-membered heterocycle with two or more heteroatoms and fused ring analogs thereof, compounds in which Ar² is a six-membered heterocyclic ring compound with one heteroatom and fused ring analogs thereof, compounds in which Ar² is a six-membered heterocycle with two or more heteroatoms and fused ring analogs thereof are provided.

20 Compounds in which which Ar² is a five-membered heterocycle with one heteroatom include, but are not limited to, compounds in which Ar² is thienyl, furyl, pyrrolyl, 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl and pyrrolidinyl and other such rings. Compounds in which Ar² is a is a fused ring analog of a 5-membered heterocycle with one heteroatom, include, but are not limited to compounds in which Ar² is benzofuryl, 25 benzothienyl (thianaphthyl), indolyl, indoliznyl, and isoindole.

Compounds in which Ar² is a 5-membered heterocycle with two or more heteroatoms and fused ring analogs thereof include, but are not limited to, compounds in which Ar² is oxazolyl, thiazolyl, imidazolyl, 2-imidazolynyl, imidaolidinyl, 1,3-dioxalanyl, pyrazolyl, 2-pyrazolynyl, pyrazolidinyl, isoxoxaolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 1H-indazolyl, benzoxazolyl, benzimidazolyl and benzothiazolyl.

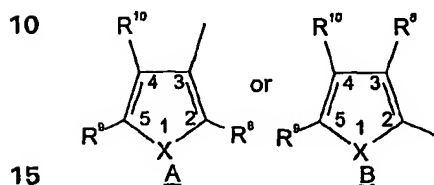
Compounds in which Ar² is a 6-membered heterocycle with one heteroatom and fused ring analogs thereof include, but are not limited to, compounds in which Ar² is pyridinyl, quinolinyl, isoquinolynl, acridine, 4H-quinolizine, 2H-pyran, 4H-pyran, and 35 piperidinyl.

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Compounds in which Ar^2 is a 6-membered heterocycle with two or more heteroatoms and fused ring analogs thereof include, but are not limited to, pyrimidinyl, pyrazinyl, piperazinyl, triazinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, morpholinyl, phenazinyl, phenythiazinyl, phenoxazinyl, quiazolinyl, quinoxalinyl, naphthyridinyl and pteridinyl.

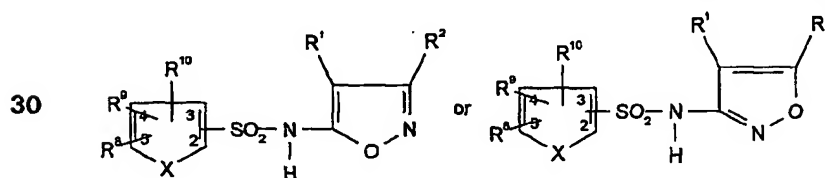
a. Ar^2 is thienyl, furyl and pyrrolyl

In certain embodiments, Ar^2 is represented by the formulae (IV):



that can be substituted at any or all positions or is an analog of compounds of formula (IV) in which the substituents form fused aromatic, aliphatic or heterocyclic rings; and in which X is NR^{11} , O, or S, and R^{11} , which is hydrogen or contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6, and is selected as defined above. R^8 , R^9 , R^{10} are selected as described above.

Thus, in certain embodiments described in detail herein, Ar^2 is thienyl, furyl, pyrrolyl or a group, such as benzofuryl, thianaphthyl or indolyl, that is a derivative of or analog, as described below, of a thienyl, furyl, pyrrolyl group, Ar^1 is preferably N-(5-isoxazolyl) or N-(3-isoxazolyl), and the compounds are represented by the formulae III:



in which R^1 , R^2 , are either (i), (ii) or (iii) as follows:

(i) R^1 and R^2 are each independently selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, aminocarbonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions are either straight

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or branched chains that contain from 1 up to about 10 carbon atoms, and the aryl portions contain from about 4 to about 14 carbons; or,

(ii) R^1 and R^2 together form $-(CH_2)_n$, where n is 3 to 6; or,

(iii) R^1 and R^2 together form 1,3-butadienyl; and

5 X, R^8 , R^9 and R^{10} are selected as defined above.

In certain embodiments, R^2 is not halide, pseudohalide or higher alkyl.

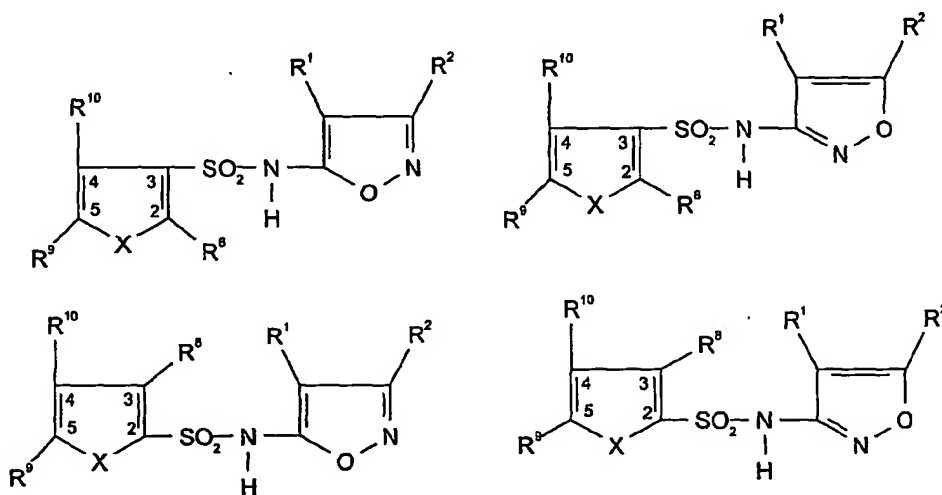
The more preferred compounds of formulae I and II provided herein are compounds in which Ar^1 is N-(5-isoxazolyl) or N-(3-isoxazolyl) that can be represented by the formulae XVIII:

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in which:

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R^1 and R^2 are either (i), (ii) or (iii) as follows:

(i) R^1 and R^2 are each independently selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl,

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aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons; or,

(ii) R^1 and R^2 together form $-(CH_2)_n$, where n is 3 to 6; or,

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(iii) R^1 and R^2 together form 1,3-butadienyl;

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- X is O, S, NH or NR¹¹ in which R¹¹, which contains up to about 30-50 atoms, generally 1 to 20 atoms, and which is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁵, S(O)_nR¹⁵ in which n is 0-2; R¹⁵ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; m is 0-2; R¹¹ and R¹⁵, are unsubstituted or are substituted with one or more substituents each independently selected from Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁶, CO₂R¹⁶, SH, S(O)_nR¹⁶ in which n is 0-2, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶; R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹², which is selected independently from R¹¹ and Z, is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2; and R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹² and R¹⁶ may be further substituted with substituents selected from Z; and R⁸, R⁹, R¹⁰, which each, when not hydrogen, contain up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, are each independently selected as follows from (i) or (ii):
- (i) R⁸, R⁹ and R¹⁰ are each independently selected from hydrogen, halide pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁸, CO₂R¹⁸, SH, S(O)_nR¹⁸ in which n is 0-2, HNOH, NR¹⁸R¹⁹, NO₂, N₃, OR¹⁸, R¹⁹NCOR¹⁸ and CONR¹⁹R¹⁸, in which R¹⁹ is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²⁰, S(O)_nR²⁰ in which n is 0-2; and R¹⁸ and R²⁰ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl, which is is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; and any of the groups set forth for R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with any substituents set forth for Z, which is is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R²¹, CO₂R²¹, SH, S(O)_nR²¹ in which n is 0-2, NHOH, NR²²R²¹, NO₂, N₃, OR²¹, R²²NCOR²¹ and CONR²²R²¹; R²² is

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- selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_nR^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl,
- 5 $C(O)R^{25}$ and $S(O)_nR^{25}$ in which n is 0-2; R^{24} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; and R^{25} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; any of the preceding groups, including R^8 , R^9 , R^{10} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} and R^{25} may be unsubstituted, except as specified, or
- 10 may be further substituted with substituents selected from Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; or
- (ii) any two of R^8 , R^9 and R^{10} form an aromatic or heteroaromatic ring or an alicyclic or heterocyclic ring, which is saturated or unsaturated, containing from
- 15 about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to 7 members, and which is unsubstituted or substituted with one or more substituents in each each substituent is independently selected from Z; and the other of R^8 , R^9 and R^{10} is selected as in (i).
- In preferred embodiments: X is S, O, NR^{11} in which R^{11} is aryl, hydrogen, or
- 20 lower alkyl, preferably, a substituted or unsubstituted aryl, particularly phenyl, preferably unsubstituted or substituted with lower alkyl or halogen hydrogen or lower alkyl; R^1 is hydrogen, halide, pseudohalide, lower alkyl or lower haloalkyl, most preferably halide; R^2 is hydrogen, lower alkyl or lower haloalkyl; and R^8 , R^9 and R^{10} are each selected independently from hydrogen, halide, pseudohalide, lower alkyl,
- 25 lower aryl, lower heterocycle, lower aralkyl, $S(O)_nR^{18}$ in which n is 0-2, $C(O)R^{18}$, CO_2R^{18} , NO_2 , OR^{18} or $CONR^{19}R^{18}$; R^{19} is preferably hydrogen, lower alkyl, and lower aryl, $C(O)R^{20}$, $S(O)_nR^{20}$ in which n is 0-2; R^{18} is preferably hydrogen, halide, lower alkyl or lower aryl, and R^{20} is preferably hydrogen, halide or lower alkyl; and Z is hydrogen, halide, pseudohalide, lower alkyl or lower pseudohaloalkyl or lower haloalkyl. In
- 30 particular, at least one of R^8 , R^9 and R^{10} is selected from methyl, phenyl, pyrazolyl, isoxazolyl, carbomethoxy, carboxamide, halide, hydrogen, isopropylphenyl, pyridyl, carboxyl, phenyl, phenylaminocarbonyl, benzenesulfonyl, lower-alkylphenylaminocarbonyl, biphenylaminocarbonyl, (lower)haloalkoxyphenyl-

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aminocarbonyl and halophenylaminocarbonyl and, preferably, two of R^8 , R^9 and R^{10} are hydrogen, halide or lower alkyl. In more preferred of these embodiments X is S.

In more preferred embodiments, two of R^8 , R^9 and R^{10} are hydrogen, halide or lower alkyl and the other is hydrogen, halide, pseudohalide, lower alkyl, lower aryl, heterolower aryl, lower aralkyl, $C(O)R^{18}$, CO_2R^{18} , NO_2 , OR^{18} or $CONR^{19}R^{18}$. In yet more preferred embodiments R^{19} is phenyl and R^{18} is hydrogen, halide or lower alkyl. In more preferred of these embodiments, two of R^8 , R^9 and R^{10} are hydrogen or lower alkyl and the other is halide, lower alkyl, $C(O)R^{18}$, CO_2R^{18} , NO_2 , OR^{18} or $CONR^{19}R^{18}$; R^{18} is hydrogen or lower alkyl. In all embodiments, R^1 is preferably halide, H, CH_3 or C_2H_5 , and R^2 is H, CH_3 , C_2H_5 , C_2F_5 or CF_3 . In yet more preferred embodiments, R^1 preferably Br, Cl or CH_3 ; R^2 is H, CH_3 , C_2H_5 , or CF_3 .

In certain preferred embodiments, R^9 and R^{10} are H, halide or lower alkyl; and R^8 is any of the above listed substituents, and particularly, when a potent ET_A antagonist is desired is a substituted aminocarbonyl. In other preferred embodiments it is preferred that R^8 and R^{10} are H or lower alkyl and R^9 is any of the above-listed substituents. In the preferred of these embodiments, R^1 is halide, H, CH_3 or C_2H_5 , and R^2 is H, CH_3 , C_2H_5 , C_2F_5 or CF_3 . In yet more preferred embodiments, R^1 is Br, Cl or CH_3 ; and R^2 is H, CH_3 , C_2H_5 , or CF_3 .

In embodiments in which ET_B antagonists are desired, it is preferred that R^8 and R^{10} are H or lower alkyl and R^9 is a heterocyclic or aromatic ring of preferably from 3 to 14, more preferably, 5 to 7, members in the ring. In particular, if X is S, R^8 and R^{10} are H or lower alkyl, and R^9 , is aryl, particularly unsubstituted or substituted phenyl, such as 4-ethylphenyl. If X is N, then R^{11} is aryl, particularly unsubstituted phenyl or substituted phenyl, such as isopropylphenyl and R^8 , R^9 and R^{10} are preferably H, halide or lower alkyl.

The most preferred compounds provided herein have an IC_{50} for ET_A receptors in the assays exemplified herein between about .002 μM and 0.1 μM (see, e.g., Table 6). These compounds include: N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-methoxyphenyl)-aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(3-methoxyphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(N-phenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-bromo-5-methyl-3-isoxazolyl)-2-(N-phenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2-(N-phenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2,5-dimethylthiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-

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(carbomethoxy)thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)thiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-biphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(2-methoxyphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(N-benzylaminocarbonyl)thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-ethylphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-biphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-methoxyphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-3-phenylthiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-4-phenylthiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-3-phenoxythiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-methylphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-isopropylphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-t-butylphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-n-butylphenyl)aminocarbonyl]thiophene-3-sulfonamide; and N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-sec-butylphenyl)aminocarbonyl]thiophene-3-sulfonamide.

Other preferred compounds include those that have an IC_{50} for ET_B receptors, as measured in the assays herein, of between about 0.05 μ M and 1 μ M. These include compounds, such as N-(4-bromo-3-methyl-5-isoxazolyl)-5-benzenesulfonylthiophene-2-sulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-1-(4'-isopropylphenyl)pyrrole-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-1-(4'-isopropylphenyl)pyrrole-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-{3-[1-methyl-5-(trifluoromethyl)pyrazolyl]}thiophene-5-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-biphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-ethylphenyl)aminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-thienylthiophene-2-sulfonamide; and N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4-ethylphenyl)thiophene-2-sulfonamide.

Other thienyl-, furyl- and pyrrole-sulfonamides provided herein include the following compounds: N-(4-chloro-3-methyl-5-isoxazolyl)-2-(phenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-5-benzylthiophene-2-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-3-benzylthiophene-2-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-3-phenethylthiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-3-styrylthiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-

isoxazolyl)-2-styrylthiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-phenoxythiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-benzenesulfonylthiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-phenylthiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-aminothiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(benzoylamino)thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-3-benzylthiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-3-phenethylthiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-benzylthiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(N-phenyl)methylaminocarbonyl]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-benzylfuran-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-(phenylthio)furan-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-(hydroxymethyl)furan-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-(carbomethoxy)furan-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2,5-dimethylfuran-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4-isopropylphenyl)thiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4-propylphenyl)thiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-3-(phenylaminocarbonyl)thiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-benzylthiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-phenylthiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(dimethylaminocarbonyl)thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(di-isopropylaminocarbonyl)thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(diethylaminocarbonyl)thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4-iso-butylphenyl)furan-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-styrylfuran-2-sulfonamide; and N-(4-bromo-3-methyl-5-isoxazolyl)-5-styrylthiophene-2-sulfonamide.

In other embodiments, the compounds are of formula XVIII, where R^8 , R^9 and R^{10} , which each contain hydrogen or up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, are each independently selected as described above, and more preferably from (i) or (ii) as follows:

(i) R^8 and R^{10} are selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{18}$, $(OAC)CH=CHR^{18}$, CO_2R^{18} , SH, $(CH_2)_iC(O)(CH_2)_nR^{18}$, $(CH_2)_i(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_iC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_i(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_iNH(CH=CH)_s(CH_2)_nR^{18}$, $C=N(OH)(CH_2)_iR^{18}$, $(CH_2)_i(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_iC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_iNH(CH_2)_nR^{18}$, $(CH_2)_iNH(CH_2)_nR^{18}$, $(CH_2)_iR^{18}$, $S(O)_mR^{18}$ in

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which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, HNOH, NR¹⁸R¹⁹, NO₂, N₃, OR¹⁸, R¹⁹NCOR¹⁸ and CONR¹⁹R¹⁸, in which R¹⁹ is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²⁰, S(O)_nR²⁰ in which n is 0-2; and

5 R¹⁸ and R²⁰ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl;

R⁸ is selected from C(O)R¹⁸, (OAC)CH=CHR¹⁸, CO₂R¹⁸, (CH₂)_rC(O)(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_rC(O)(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sC(O)(CH₂)_nR¹⁸, (CH₂)_rNH(CH=CH)_s(CH₂)_nR¹⁸, C=N(OH)(CH₂)_rR¹⁸, (CH₂)_r(CH=CH)_sNH(CH₂)_nR¹⁸, (CH₂)_rC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rR¹⁸, in which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, in which R¹⁸ is aryl, preferably phenyl;

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where any of the groups set forth for R⁸, R⁹ and R¹⁰ are unsubstituted or

15 substituted with any substituents set forth for Z, which is hydrogen, halide, pseudoalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R²¹, CO₂R²¹, SH, S(O)_nR²¹ in which n is 0-2, NHOH, NR²²R²¹, NO₂, N₃, OR²¹, R²²NCOR²¹ and CONR²²R²¹; R²² is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²³ and S(O)_nR²³ in which n is 0-2; and R²¹ and R²³ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; or

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(ii) any two of R⁸, R⁹ and R¹⁰ form an aryl, aromatic ring, heteroaromatic ring, carbocyclic or heterocyclic ring, which is saturated or unsaturated, containing from

25 about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to 7 members that is substituted with one or more substituents, each substituent being independently selected from Z; the other of R⁸, R⁹ and R¹⁰ is selected as from the groups set forth for R⁹ and R¹⁰ in (i); and the heteroatoms are NR¹¹, O, or S.

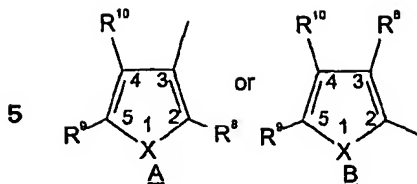
In certain embodiments, Ar² is not 5-halo-3-loweralkylbenzo[b]thienyl, 5-halo-3-loweralkylbenzo[b]furyl, 5-halo-3-loweralkylbenzo[b]pyrrolyl. In other embodiments, if

30 R⁸ is (CH₂)_rC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rR¹⁸, particularly if r is 0 and/or n is 0, and R¹⁸ is aryl, particularly phenyl, then R¹⁸ must have two or more substituents, with preferably at least one ortho substituent.

In these embodiments, Ar² is, thus, represented by the formulae (IVA and IVB):

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10 that can be substituted at any or all positions or is an analog of compounds of formula (IV) in which the substituents form fused aromatic, aliphatic or heterocyclic rings; and in which X is NR¹¹, O, or S, and R¹¹, which is hydrogen or contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6, and is selected as defined above. R⁸, R⁹, R¹⁰ are selected as described above.

15 In the embodiments provided herein, when R⁸, R⁹ and R¹⁰ are selected as in (i), above, R⁸ is preferably selected from among (CH₂)_rC(O)(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_rC(O)(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sC(O)(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sNH(CH₂)_nR¹⁸, C=N(OH)(CH₂)_rR¹⁸, (CH₂)_rC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH=CH)_s(CH₂)_nR¹⁸,
 20 (CH₂)_rC(O)NH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rR¹⁸.

In certain of these embodiments, if R⁸ is (CH₂)_rC(O)NH(CH₂)_nR¹⁸, (CH₂)_rC(O)NH(CH₂)_nR¹⁸, or (CH₂)_rR¹⁸, and R¹⁸ is phenyl, the phenyl group is substituted at least two positions, and preferably, at least one of those positions is ortho.

In preferred of these compounds, R¹⁸ is aryl or heteroaryl, preferably having 5 or
 25 6 members in the ring, more preferably phenyl or pyrimidinyl, most preferably phenyl. R⁹ and R¹⁰ are preferably hydrogen, halide, loweralkyl, or halo loweralkyl.

In preferred embodiments: X is S, O, NR¹¹ in which R¹¹ is aryl, hydrogen, or loweralkyl, preferably, a substituted or unsubstituted aryl, particularly phenyl, preferably unsubstituted or substituted with loweralkyl or halogen hydrogen or loweralkyl; R¹ is
 30 hydrogen, halide, pseudohalide, loweralkyl or lower haloalkyl, most preferably halide; R² is hydrogen, loweralkyl or lower haloalkyl.

In more preferred embodiments, two of R⁹ and R¹⁰ are hydrogen, halide or loweralkyl and R⁸ is C(O)NHR¹⁸ or C(O)CH₂R¹⁸ in which R¹⁸ is a phenyl group that is substituted at least two positions, most preferably at least one substituent at the ortho
 35 position and also 3,4 or 4,5 alkylenedioxy substituents. In more preferred of these embodiments X is S.

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In all embodiments, R^1 is preferably halide, H, CH_3 or C_2H_5 , and R^2 is H, CH_3 , C_2H_5 , C_2F_5 or CF_3 . In yet more preferred embodiments, R^1 preferably Br, Cl or CH_3 ; R^2 is H, CH_3 , C_2H_5 , or CF_3 .

- In other embodiments two of R^8 , R^9 and R^{10} form a ring so that Ar^2 is
- 5 benzo[b]thienyl, benzo[b]furyl, or indolyl, with the proviso that there is one or more substituents and they are other than 5-halo and 3-loweralkyl, and the other of R^8 , R^9 and R^{10} is selected from aryl, $(CH_2)_nR^{18}$, $C(O)R^{18}$, CO_2R^{18} , $NR^{18}R^{19}$, SH, $S(O)_nR^{18}$ in which n is 0-2, HNOH, NO_2 , N_3 , OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{18}R^{19}$. Ar^2 may be further
- 10 substituted with any of the groups set forth for R^8 , R^9 and R^{10} , and are preferably selected from among alkyl, alkoxy, alkoxyalkyl, aryl, alkylaryl, aminoalkyl, arylamino, aryl-substituted amino, and NR^{11} .

- In embodiments in which ET_B antagonists are desired, it is preferred that R^8 and R^{10} are H or loweralkyl and R^9 includes heterocyclic or aromatic ring of preferably from 3 to 14, more preferably, 5 to 7, members in the ring. In particular, if X is S, R^8 and R^{10}
- 15 are H or loweralkyl, and R^9 , includes an aryl group, particularly a substituted phenyl, such as a 2-loweralkyl substituent. The aryl portion is substituted with groups such as alkyl, alkoxy, alkoxyalkyl, halogen, alkylenedioxy, particularly methylenedioxy, amino, nitro and other such groups. The alkyl substituents are preferably loweralkyl, more preferably containing 1-3 carbons.
- 20 If X is NR^{11} , then R^{11} is aryl, particularly unsubstituted phenyl or substituted phenyl, such as isopropylphenyl.

Other preferred compounds, which are ET_B active, are those in which Ar^2 has formula IVB in which R^9 is aryl or Z-substituted aryl, particularly phenyl, and Z is loweralkyl or loweralkoxy.

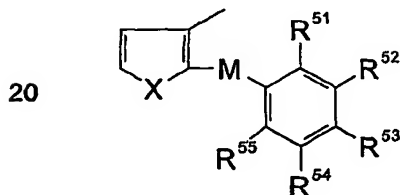
- 25 In all embodiments of all of the compounds herein R^1 is preferably halide or loweralkyl, most preferably Br, and the compounds are, with reference to formulae IV, 2- or 3-sulfonamides, particularly thiophene sulfonamides. In certain embodiments provided herein, Ar^2 is a benzo[b]thienyl, benzo[b]furyl or indolyl (benzo[b]pyrrolyl) group and the compounds provided herein are preferably benzo[b]thienyl-, benzo[b]furyl- or
- 30 indolylsulfonamides. Benzo[b]thiophene, benzo[b]furyl and indolyl 2- or 3-sulfonamides are among the compounds preferred herein. The benzo[b]thiophene, benzo[b]furyl and indolyl 2- or 3-sulfonamides provided herein are selected with the proviso that the benzene group has at least one substituent and that substituent is other than 5-halo and 3-loweralkyl.

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Compounds of particular interest include those of formula II in which Ar² is a phenyl-, benzothienyl, benzofuryl or indolyl [benzopyrrolyl] group or in which Ar² is a substituted phenylaminocarbonylthienyl, substituted phenylaminocarbonylfuryl, substituted phenylaminocarbonylpyrrolyl group or Ar² is phenylacetylthiophene, phenylacetylfuran, or phenylacetylpyrrole, or is an acetoxystyrylthiophene, acetoxystyrylfuran or acetoxystyrylpyrrole. In certain embodiments, Ar² is a substituted phenylaminocarbonylthienyl, substituted phenylaminocarbonylfuryl, substituted phenylaminocarbonylpyrrolyl group in which there are at least two substituents on the phenyl ring.

The most preferred compounds provided herein have an IC₅₀ for ET_A receptors in the assays exemplified herein less than 0.1 μM, more preferably less than 0.01 μM, and more preferably less than 0.001 (see, e.g., Table 6 for representative experimental results), when measured at 4° C, as described in the Examples. When measured at 24° C, the IC₅₀ concentrations are somewhat higher (2- to 10-fold; see, Table 1 for some comparative values).

Among the preferred compounds of interest herein are those in which Ar² has formula XIX:



in which M is (CH₂)_mC(O)(CH₂)_r, (CH₂)_mC(O)NH(CH₂)_r, (CH₂)_m(CH=CH)(CH₂)_r, (CH₂)_mC(O)(CH₂)_sNH(CH₂)_r, (CH₂)_m(CH=CH)(CH₂)_r, C=N(OH)(CH₂)_r, (CH₂)_mC(O)(CH=CH)_sNH(CH₂)_r, CH(OH)(CH₂)_r, CH(CH₃)C(O)(CH₂)_r, CH(CH₃)C(O)(CH₂)_m(CH=CH)(CH₂)_r, (CH₂)_r, (CH₂)_rO, C(O)O, in which m, s and r are each independently 0 to 6, preferably 0 to 3, more preferably M is (CH₂)_mC(O)(CH₂)_r, (CH₂)_mC(O)NH(CH₂)_r, (CH₂)_m(CH=CH)(CH₂)_r, (CH₂)_mC(O)(CH₂)_sNH(CH₂)_r, (CH₂)_m(CH=CH)(CH₂)_r, C=N(OH)(CH₂)_r, CH(OH)(CH₂)_r, (CH₂)_r, (CH₂)_rO, C(O)O;

R⁵¹, R⁵², R⁵³, R⁵⁴ and R⁵⁵ are each independently selected from

(i) or (ii) as follows:

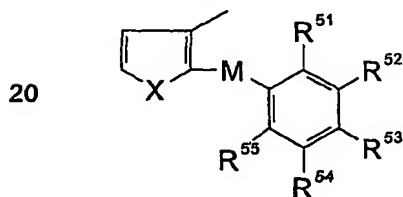
(i) R⁵¹, R⁵², R⁵³, R⁵⁴ and R⁵⁵ are each independently selected from among H, OH, NHR³⁸, CONR³⁸R³⁹, NO₂, cyano, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, haloalkyl, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, alkylcarbonyl, alkenylthio, alkenylamino, alkenyloxy,

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Compounds of particular interest include those of formula II in which Ar² is a phenyl-, benzothienyl, benzofuryl or indolyl [benzopyrrolyl] group or in which Ar² is a substituted phenylaminocarbonylthienyl, substituted phenylaminocarbonylfuryl, substituted phenylaminocarbonylpyrrolyl group or Ar² is phenylacetylthiophene, phenylacetylfuran, or phenylacetylpyrrole, or is an acetoxystyrylthiophene, acetoxystyrylfuran or acetoxystyrylpyrrole. In certain embodiments, Ar² is a substituted phenylaminocarbonylthienyl, substituted phenylaminocarbonylfuryl, substituted phenylaminocarbonylpyrrolyl group in which there are at least two substituents on the phenyl ring.

The most preferred compounds provided herein have an IC₅₀ for ET_A receptors in the assays exemplified herein less than 0.1 μM, more preferably less than 0.01 μM, and more preferably less than 0.001 (see, e.g., Table 6 for representative experimental results), when measured at 4° C, as described in the Examples. When measured at 24° C, the IC₅₀ concentrations are somewhat higher (2- to 10-fold; see, Table 1 for some comparative values).

Among the preferred compounds of interest herein are those in which Ar² has formula XIX:



in which M is (CH₂)_mC(O)(CH₂)_r, (CH₂)_mC(O)NH(CH₂)_r, (CH₂)_m(CH=CH)(CH₂)_r, (CH₂)_mC(O)(CH₂)_sNH(CH₂)_r, (CH₂)_m(CH=CH)(CH₂)_r, C=N(OH)(CH₂)_r, (CH₂)_mC(O)(CH=CH)_sNH(CH₂)_r, CH(OH)(CH₂)_r, CH(CH₃)C(O)(CH₂)_r, CH(CH₃)C(O)(CH₂)_m(CH=CH)(CH₂)_r, (CH₂)_r, (CH₂)_rO, C(O)O, in which m, s and r are each independently 0 to 6, preferably 0 to 3, more preferably M is (CH₂)_mC(O)(CH₂)_r, (CH₂)_mC(O)NH(CH₂)_r, (CH₂)_m(CH=CH)(CH₂)_r, (CH₂)_mC(O)(CH₂)_sNH(CH₂)_r, (CH₂)_m(CH=CH)(CH₂)_r, C=N(OH)(CH₂)_r, CH(OH)(CH₂)_r, (CH₂)_r, (CH₂)_rO, C(O)O;

R⁵¹, R⁵², R⁵³, R⁵⁴ and R⁵⁵ are each independently selected from

(i) or (ii) as follows:

(i) R⁵¹, R⁵², R⁵³, R⁵⁴ and R⁵⁵ are each independently selected from among H, OH, NHR³⁸, CONR³⁸R³⁹, NO₂, cyano, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, haloalkyl, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, alkylcarbonyl, alkenylthio, alkenylamino, alkenyloxy,

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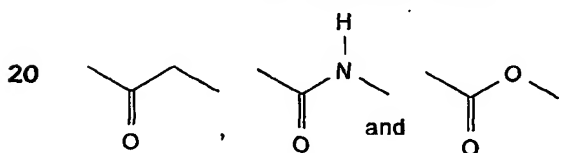
alkenyl sulfinyl, alkenylsulfonyl, alkoxycarbonyl, arylaminocarbonyl, alkylaminocarbonyl, aminocarbonyl, (alkyl-aminocarbonyl)alkyl, carboxyl, carboxyalkyl, carboxyalkenyl, alkylsulfonylaminoalkyl, cyanoalkyl, acetyl, acetoxymethyl, hydroxymethyl, alkoxyalkoxy, hydroxyalkyl, (acetoxymethyl)alkoxy, (hydroxymethyl)alkoxy and formyl; or

- 5 (ii) at least two of R^{51} , R^{52} , R^{53} , R^{54} and R^{55} , which substitute adjacent carbons on the ring, together form alkylenedioxy, alkylenethioxy or alkylenedithioxy (i.e. $-O-(CH_2)_n-O-$, $-S-(CH_2)_n-O-$, $-S-(CH_2)_n-S-$, where n is 1 to 4, preferably 1 or 2,) which is unsubstituted or substituted by replacing one or more hydrogens with halide, loweralkyl, loweralkoxy or halo loweralkyl, and the others of R^{51} , R^{52} , R^{53} , R^{54} and R^{55}
- 10 are selected as in (i); and

R^{38} and R^{39} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, haloalkyl, alkylaryl, heterocycle, arylalkyl, arylalkoxy, alkoxy, aryloxy, cycloalkyl, cycloalkenyl and cycloalkynyl, and is preferably hydrogen, loweralkyl, loweralkoxy and lowerhaloalkyl.

- 15 In certain embodiments, when M is $(CH_2)_mC(O)NH(CH_2)_n$, then at least two of R^{51} , R^{52} , R^{53} , R^{54} and R^{55} are not hydrogen.

M is most preferably selected from



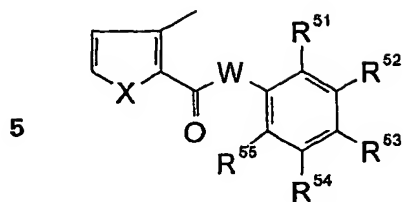
- 25 In general, however, in all of these compounds in which Ar^2 has formula V or VI or in which R^8 includes an aryl group, regardless of the selection of M , it is preferred that the aryl substituent have more than one substituent or at least one substituent in the ortho position. Aryl is preferably phenyl that is preferably substituted at the ortho position and, more preferably at at least one additional position, particularly 4 and 6, or
- 30 adjacent positions, such as 3,4 or 4,5 when the substituents are linked to form an alkylenedioxy (or analog thereof in which one or both oxygens is(are) replaced with S.

In certain compounds herein, at least one of R^{51} and R^{55} is other than hydrogen.

In more preferred compounds, M is $C(O)CH_2$, $C(O)NH$, $-CH=CH-$, $CH_2CH_2C(O)(CH)_2$, $CH_2CHC(O)CH_2$, and Ar^2 most preferably has formula XX:

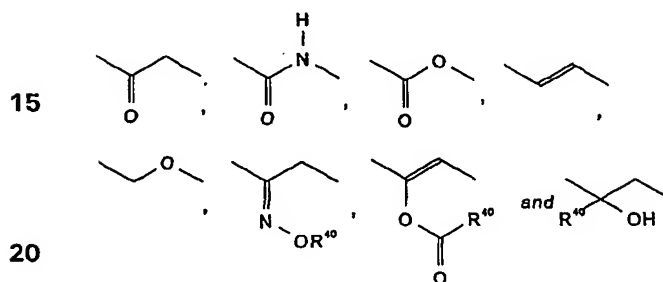
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10 in which W is CH₂ or NH.

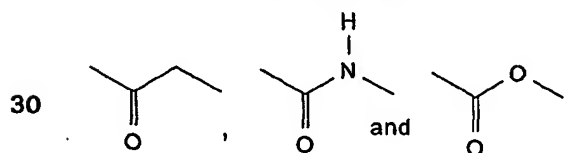
M is even more preferably selected from among:



in which R⁴⁰ is preferably hydrogen, alkyl, alkoxy, alkoxyalkyl, haloalkyl, and more preferably loweralkyl, loweralkoxy, or halo loweralkyl, and is more preferably hydrogen

25 or loweralkyl, particularly methyl or ethyl, and is most preferably hydrogen.

M is most preferably:



In preferred compounds R⁵¹, R⁵², R⁵³, R⁵⁴ and R⁵⁵ are selected from (i) or (ii):

35 (i) R⁵¹, R⁵², R⁵³, R⁵⁴ and R⁵⁵ are each independently selected from loweralkyl, haloloweralkyl, phenyl, alkoxy, loweralkylsulfonylaminoloweralkyl, cyanoloweralkyl, acetyl, loweralkoxycarbonyl, cyano, OH, acetoxyloweralkyl, hydroxy loweralkyl, acetoxy loweralkoxy or loweralkoxycarbonyl; or

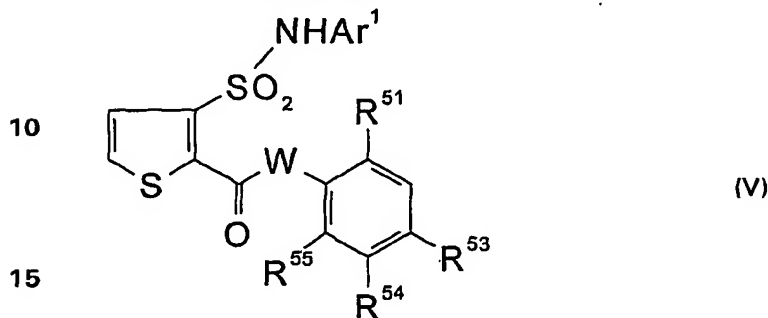
(ii) R⁵² and R⁵³ or R⁵³ and R⁵⁴ form alkylene dioxy, preferably methylenedioxy, and the others of R⁵¹, R⁵², R⁵³, R⁵⁴ and R⁵⁵ are selected as in (i).

40 In preferred embodiments, R⁵¹, R⁵³, R⁵⁵ are other than hydrogen and are preferably loweralkyl or lower alkoxy, or R⁵¹ or R⁵⁵ is other than hydrogen, preferably loweralkyl or lower alkoxy, and R⁵² and R⁵³ or R⁵³ and R⁵⁴ form methylenedioxy.

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In particular, Ar^1 is a five or six membered substituted or unsubstituted aromatic or heteroaromatic ring or a fused bicyclic substituted or unsubstituted aromatic or heteroaromatic ring, preferably 3- or 5-isoxazolyl, benzo-2,1,3-thiadiazol-5-yl, 2-pyrazinyl or benzo-2,1,3-oxadiazol-5-yl.

5 In one embodiment, the sulfonamides have formula V:



or the corresponding thiophene-2-sulfonamides as defined above.

20 Ar^1 is a substituted or unsubstituted monocyclic or polycyclic, preferably a monocyclic or fused bicyclic, aryl group with one or more substituents, selected from, for example, H, NH_2 , halide, pseudohalide, alkyl, alkylcarbonyl, formyl, an aromatic or heteroaromatic group, alkoxyalkyl, alkylamino, alkylthio, arylcarbonyl, aryloxy, arylamino, arylthio, haloalkyl, haloaryl, carbonyl, in which the aryl and alkyl portions are
 25 unsubstituted or substituted with any of the preceding groups, and straight or branched chains of from about 1 up to about 10-12 carbons, preferably, 1 to about 5 or 6 carbons. The substituents are preferably H, NH_2 , halide, CH_3 , CH_3O or another aromatic group. In particular, Ar^2 is a five or six membered substituted or unsubstituted aromatic or heteroaromatic ring or a fused bicyclic substituted or unsubstituted aromatic or heteroaromatic ring, preferably 3- or 5-isoxazolyl, benzo-2,1,3-thiadiazol-5-yl, 2-
 30 pyrazinyl or benzo-2,1,3-oxadiazol-5-yl, more preferably 4-chloro-3-methyl-5-isoxazolyl or 4-chloro-5-methyl-3-isoxazolyl; W is $-\text{NH}-$, $=\text{NCOR}^{16}$, $=\text{NCO}_2\text{R}^{16}$, $-\text{NHC}(\text{R}^{12})(\text{R}^{16})-$ or is $-\text{CH}_2-$ when R^{54} is hydroxyl.

R^{54} is selected from the group consisting of substituted and unsubstituted alkyl, hydroxyl, substituted and unsubstituted alkoxy, $\text{OC}(\text{O})\text{R}^{16}$, $\text{OCO}_2\text{R}^{16}$, $\text{NR}^{12}\text{R}^{16}$ and $\text{S}(\text{O})_n\text{R}^{16}$ in which n is 0-2; preferably alkoxycarbonylalkyl, carboxyalkyl, dialkylaminoalkyl, alkylsulfonylamino and aminosulfonyl.

R^{51} , R^{53} and R^{55} , which are preferably alkyl, haloalkyl, polyhaloalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl,

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cycloalkylalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, more preferably lower alkyl, lower alkenyl, lower alkynyl, or aryl, most preferably methyl.

In preferred embodiments of the compounds of formula V, Ar¹ is 3- or 5-isoxazolyl, benzo-2,1,3-thiadiazol-5-yl, 2-pyrazinyl or benzo-2,1,3-oxadiazol-5-yl, more preferably 3-methoxy-2-pyrazinyl, 3,4-dimethyl-5-isoxazolyl, 4-chloro-3-methyl-5-isoxazolyl or 4-chloro-5-methyl-3-isoxazolyl; W is -NH-, =NCO₂R¹⁶, or is -CH₂- when R⁵⁴ is hydroxyl; R⁵¹, R⁵³ and R⁵⁵ are methyl; and R⁵⁴ is selected from the group consisting of substituted and unsubstituted alkyl, hydroxyl, substituted and unsubstituted alkoxy, OC(O)R¹⁶, OCO₂R¹⁶, NR¹²R¹⁶ and S(O)_nR¹⁶ in which n is 0-2; preferably alkoxy-carbonylalkyl, carboxyalkyl, dialkylaminoalkyl, alkylsulfonamino and aminosulfonyl.

R⁵⁴ is, in certain of these embodiments, methoxy, methoxycarbonylmethoxy, 2-(2-methoxyethoxy)ethoxyacetoxymethyl, 2-hydroxyethoxy, N,N-dimethylthiocarbonyloxy, N,N-dimethylthiocarbonyloxymethyl, dimethylamino, pyrrolidinyl, acetoxymethyl, hydroxymethyl, carboxymethyl, methanesulfonamino, N,N-dimethylaminomethyl, SO₂NH₂, or methoxycarbonylmethyl.

R⁵⁴, in more preferred embodiments, does not contain a cyano group and is, for example, methoxy, methoxycarbonylmethoxy, 2-(2-methoxyethoxy)ethoxyacetoxymethyl, 2-hydroxyethoxy, N,N-dimethylthiocarbonyloxy, N,N-dimethylthiocarbonyloxymethyl, dimethylamino, pyrrolidinyl, acetoxymethyl, methoxycarbonylmethyl, hydroxy or acetoxymethyl.

Among the compounds of formula V are:

N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-pyrrolidinyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-dimethylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(N,N-dimethylthiocarbonyloxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(N,N-dimethylthiocarbonyloxy)-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(2-hydroxyethoxy)-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(2-(2-methoxyethoxy)ethoxy)acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfon-

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- amide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonylmethoxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-carboxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-

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- isoxazolyl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 5 N-(3,4-dimethyl-5-isoxazolyl)-2-(3-carboxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-
- 10 (benzo-2,1,3-thiadiazol-5-yl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocar-
- 15 bonyl)thiophene-3-sulfonamide; N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(benzo-2,1,3-thiadiazol-
- 20 5-yl)-2-(3-carboxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3-methoxy-2-pyrazinyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3-methoxy-2-
- 25 pyrazinyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3-methoxy-2-pyrazinyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3-methoxy-2-pyrazinyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3-methoxy-2-pyrazinyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfona-
- 30 mide; N-(3-methoxy-2-pyrazinyl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3-methoxy-2-pyrazinyl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3-methoxy-2-pyrazinyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3-methoxy-2-pyrazinyl)-2-(3-carboxy-2,4,6-trimethylphenylaminocar-

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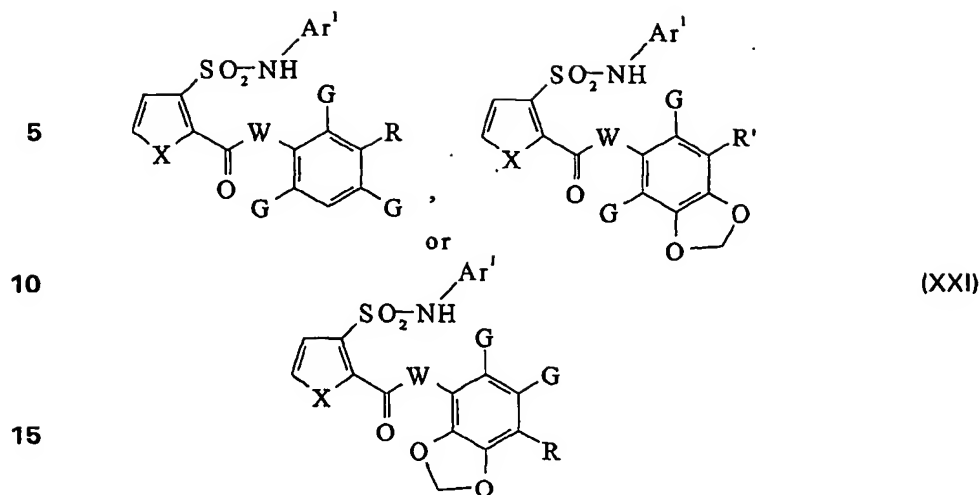
bonyl)thiophene-3-sulfonamide; N-(3-methoxy-2-pyrazinyl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(3-methoxy-2-pyrazinyl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(1-methyl-1-phenyl-1-ethylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-((R)-1-phenyl-1-ethylaminocarbonyl)thiophene-3-sulfonamide; and N-(4-chloro-3-methyl-5-isoxazolyl)-2-((S)-1-phenyl-1-ethylaminocarbonyl)thiophene-3-sulfonamide.

Among the more preferred compounds of formula II are:

N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonylmethoxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(2-(2-methoxyethoxy)ethoxy)acetoxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(2-hydroxyethoxy)-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(N,N-dimethylthiocarbonyloxy)-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(N,N-dimethylthiocarbonyloxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-dimethylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-pyrrolidinyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; and N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide.

In another embodiment, the sulfonamides have formula XXI:

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or the corresponding thiophene-2-sulfonamides as defined above, where Ar^1 is a

20 substituted or unsubstituted monocyclic or polycyclic, preferably a monocyclic or fused bicyclic, aryl group with one or more substituents, selected from, for example, H, NH_2 , halide, pseudohalide, alkyl, alkylcarbonyl, formyl, an aromatic or heteroaromatic group, alkoxyalkyl, alkylamino, alkylthio, arylcarbonyl, aryloxy, arylamino, arylthio, haloalkyl, haloaryl, carbonyl, in which the aryl and alkyl portions, are unsubstituted or substituted

25 with any of the preceeding groups, and straight or branched chains of from about 1 up to about 10-12 carbons, preferably, 1 to about 5 or 6 carbons. The substituents are preferably H, NH_2 , halide, CH_3 , CH_3O or another aromatic group. In particular, Ar^1 is a five or six membered substituted or unsubstituted aromatic or heteroaromatic ring or a fused bicyclic substituted or unsubstituted aromatic or heteroaromatic ring, preferably 3-

30 or 5-isoxazolyl, benzo-2,1,3-thiadiazol-5-yl, 2-pyrazinyl or benzo-2,1,3-oxadiazol-5-yl;

X is S, O or NR^{11} ;

each G and R, which are selected from among the $\text{R}^1\text{-R}^6$ as defined above, are preferably independently selected from lower alkyl, CN , $-(\text{CH}_2)_x\text{C}(\text{O})(\text{CH}_2)_x$, $-(\text{CH}_2)_x$, $(\text{CH}_2)_x\text{N}$ -lower alkyl, $-(\text{CH}_2)_x\text{C}(\text{O})\text{NH}_2$, a D-, L- or racemic amino acid, a primary or

35 secondary amide, O-glycoside, a hexose or ribose, $-\text{S}(\text{O})_2\text{NH}_2$, hydroxy, alkoxy, alkoxy carbonyl, acetoxyalkyl, $-(\text{CH}_2)_x\text{COOH}$; $-(\text{CH}_2)_x\text{COOH}-$, CO_2 -lower alkyl, CN , heteroaryl, $-\text{COC}(\text{O})(\text{CH}_2)_x\text{CH}_3$, $-(\text{CH}_2)_x\text{N}(\text{CH}_3)_2$, a sulfonyl chloride, $\text{S}(\text{O})_2\text{NHR}^{50}$, alkylaryl, alkylheteroaryl, $\text{C}(\text{O})\text{NHR}^{50}$, $-(\text{CH}_2)_x\text{OH}$, $-\text{C}(\text{O})\text{N}(\text{H})\text{N}(\text{H})\text{M}'$;

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R^{50} is hydrogen, lower alkyl, lower alkoxy; M' is H or R^{50} ; R' is selected from hydrogen, G and R; W is $=C(\text{halo})_2$, $=N(H)$, $-(CH_2)_x-$, $=N(\text{lower alkyl})$, $-C(O)-$, $=C(\text{lower alkyl})_2$, and x is 0-3.

In particular, in these embodiments compounds where: R, G and R' are selected
 5 where the amino acid is L-Asp or L-Glu; the hexose is D-mannose, the heteroaryl is triazolyl, and X is S are of interest. Also of interest are compounds in which:

W is $=CH_2$, $=NH$, $=NCH_3$, $=NCH_2CH_3$, $=C(CH_3)_2$ or CF_2 ; and

G is $-CH_3$, $-CN$, $-COCH_3$, $-CH_2CH_3$, $-(CH_2)_xCO_2H$.

Among these compounds are:

- 10 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonyl-2,4,6-trimethylphenyl-aminocarbonyl)thiophene-3-sulfonamide; N^2 -(3-cyanomethyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; methyl-2-(3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylphenyl)acetate; 2-(3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylphenyl)acetic acid; N^2 -(3-acetyloxymethyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N^2 -(3-hydroxymethyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N^2 -(3-dimethylaminomethyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide
- 15 trifluoroacetate; N^2 -(3-(4,5-dihydro-1,3-oxazol-2-yl)-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; 3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylbenzoic acid; N-[3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylbenzoyl]glutamic acid; N-[3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylbenzoyl]aspartic acid; N-[2-(3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylphenyl)acetyl]glutamic acid; N-[2-(3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylphenyl)acetyl]aspartic acid; N^2 -(3-cyano-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; 2-(3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylphenoxy)acetic acid; N^2 -(3-alkylsulfonamido-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N^2 -(3-arylsulfonamido-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N^2 -(3-sulfamoyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N^2 -(3-
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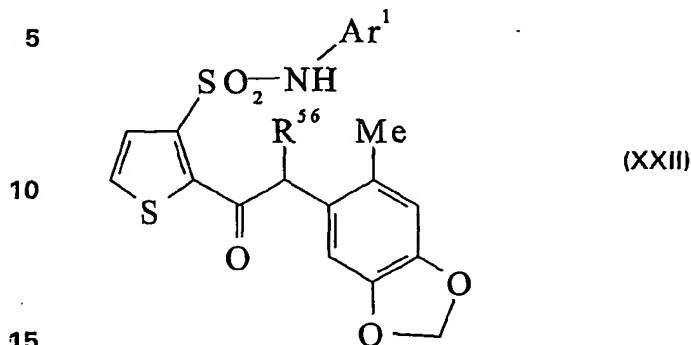
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- alkylsulfamoyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N²-(3-arylsulfamoyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N²-(3-(1H-1,2,3,4-tetraazol-5-ylmethyl)-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N²-(3-(2-pyridylmethyl)-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N²-(3-hydrazinocarbonyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N²-(3-aminomethyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; N²-(3-(α-D-mannopyranosyloxymethyl)-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide; 5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-cyano-6-methylbenzo[d][1,3]dioxole; 5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-6-cyano-4-methylbenzo[d][1,3]dioxole; 2-(5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-methylbenzo[d][1,3]dioxole)-6-acetic acid; 5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-acetyl-6-methylbenzo[d][1,3]dioxole; 5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-6-acetyl-4-methylbenzo[d][1,3]dioxole; 5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-7-cyano-4,6-dimethylbenzo[d][1,3]dioxole; 6-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-5,7-dimethylbenzo[d][1,3]dioxole-4-carboxylic acid; 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-5,6-dimethylbenzo[d][1,3]dioxole-4-carboxylic acid; 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-cyano-5,6-dimethylbenzo[d][1,3]dioxole; 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-acetyl-5,6-dimethylbenzo[d][1,3]dioxole; 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-carboxamido-5,6-dimethylbenzo[d][1,3]dioxole; 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-aminomethyl-5,6-dimethylbenzo[d][1,3]dioxole; 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-dimethylaminomethyl-5,6-dimethylbenzo[d][1,3]dioxole; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocar-

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bonyl)thiophene-3-sulfonamide; and N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide.

In another embodiment, the sulfonamides have formula XXII:



or the corresponding thiophene-2-sulfonamides as defined above, and Ar¹ is defined as above. Ar¹ is preferably benzo-2,1,3-oxadiazol-5-yl or 2-methoxy-3-pyrazinyl when R⁵⁶ is H; and R⁵⁶ is H, or substituted or unsubstituted alkyl or aryl, preferably H or substituted or unsubstituted lower alkyl, more preferably methyl or carboxymethyl.

In other embodiments of formula (IV), Ar¹ is preferably benzo-2,1,3-oxadiazol-5-yl or 2-methoxy-3-pyrazinyl when R⁵⁶ is H and

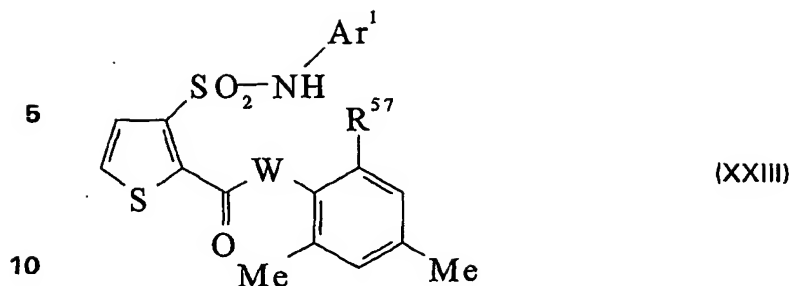
R⁵⁶ is H, or substituted or unsubstituted alkyl or aryl, preferably H or substituted or unsubstituted lower alkyl, more preferably methyl or carboxymethyl.

Thus, preferred compounds of formula IV include:

N-(benzo-2,1,3-oxadiazol-5-yl)-2-(2-methyl-4,5-methylenedioxyphenylacetyl)thiophene-3-sulfonamide; N-(3-methoxy-2-pyrazinyl)-2-(2-methyl-4,5-methylenedioxyphenylacetyl)thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(2-methyl-4,5-methylenedioxyphenyl)propanoyl)thiophene-3-sulfonamide; and N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxyl-2-(2-methyl-4,5-methylenedioxyphenyl)propanoyl)thiophene-3-sulfonamide.

In another embodiment, the sulfonamides have formula XXIII:

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or the corresponding thiophene-2-sulfonamides as defined above.

- 15 Ar¹ is defined as above and is preferably 4-chloro-3-methyl-5-isoxazolyl; W is NH; and R⁵⁷ is selected from the group consisting of aryl, heteroaryl, heterocycle, OH, CN, C(O)R¹⁶, CO₂R¹⁶, SH, S(O)_nR¹⁶ in which n is 0-2, a D, L or racemic amino acid, a ribose or hexose, an O-glycoside, a sulfonyl chloride, -(CH₂)_xOH, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶; R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl,
- 20 alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹² is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2; R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R¹², R¹⁵ and R¹⁶ may be further
- 25 substituted with the any of the groups set forth for Z; R⁵⁷ is preferably CONH², COOH, or phenyl.

Preferred embodiments of the compounds of formula XXIII are those wherein Ar¹ is 4-chloro-3-methyl-5-isoxazolyl; W is NH; and R⁵⁷ is CONH², COOH, or phenyl.

- It is understood that 4-bromo or 4-chloro groups can be replaced by other 4-halo substituents or other suitable substituents for R¹, such as alkyl. Among the preferred
- 30 compounds of formula (XXIII) are:

- N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2,3,4-trimethoxy-6-cyano)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylamino-
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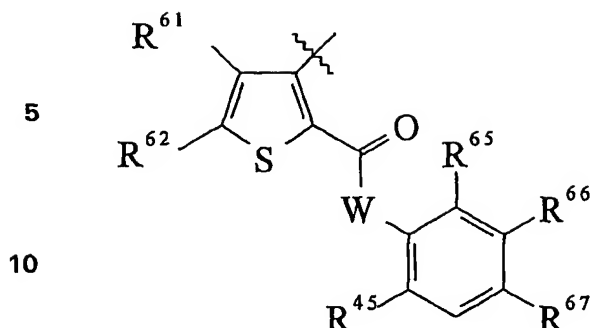
- carbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, trifluoroacetic acid salt, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(α -methyl-2-methyl-4,5-(methylenedioxy)phenylacetyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(α -carboxymethyl-2-methyl-4,5-(methylenedioxy)phenylacetyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-carbamoyl-4,6-dimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-carboxyl-4,6-dimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-phenyl-4,6-dimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, and N-(4-chloro-3-methyl-5-isoxazolyl)-2-(pentamethylphenylaminocarbonyl)thiophene-3-sulfonamide.

In preferred embodiments, Ar² has the formula:

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15 where R⁶¹ and R⁶² are hydrogen, or are each independently selected from halo, cyano, cyanoalkyl, C(O)R⁴¹, alkyl, alkenyl, cycloalkyl and aryl, or R⁶¹ and R⁶² together form alkylene; W is O, NH or CH₂;

R⁶⁵, R⁶⁶ and R⁶⁷ are each independently selected as in (i) or (ii):

(i) R⁶⁶ is hydrogen, unsubstituted alkyl, hydroxy, unsubstituted alkoxy, C(O)R⁴¹, carbamoyloxy or alkoxy carbonyloxy, and

R⁶⁵ and R⁶⁷ are each independently selected from hydrogen, unsubstituted alkyl, hydroxy, C(O)R⁴¹, carbamoyloxy and alkoxy carbonyloxy; or

(ii) if at least one of R^{61} and R^{62} is not hydrogen, then any two may form alkylenedioxy, and the other is selected as in (i); and

25 R^{45} is selected from among alkyl, $C(O)R^{41}$, $(CH_2)_xOH$ and $CH(OH)(CH_2)_xCH_3$ in which x is 0-6, $S(O)_nR^{41}$ in which n is 0-2 and $C(=NR^{43})R^{41}$; R^{41} is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, alkylamino, dialkylamino, arylamino, diarylamino, (aryl)(alkyl)amino, alkylsulfonylamino, arylsulfonylamino, (alkylsulfonyl)(alkyl or aryl)amino or (arylsulfonyl)(alkyl or aryl)amino; and R^{43} is selected from hydroxy, alkoxy, alkyl and aryl. R^{41} and R^{43} are unsubstituted or substituted with one or more substituents selected from Y, which is defined as alkoxy, halide, pseudohalide, alkylcarbonyl, arylcarbonyl, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryloxy carbonyl or hydroxy. Also of interest are the corresponding 3-acyl-2-thiophenesulfonamides.

35 If the aryl group is tetrasubstituted, it will preferably be substituted at the 2, 4 and 6 positions, and one of these substituents will be a polar group, such as hydroxyl, acetoxy, carboxyl and carboxamide. If the aryl group is substituted at the 2, 4 and 6 positions with nonpolar groups, such as alkyl groups, more specifically methyl groups, then the aryl group will preferably be penta- or hexasubstituted. In pentasubstituted

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aryl groups, the fifth substituent will be at the 3 position and will preferably be a polar group, such as hydroxyl, acetoxy, carboxyl and carboxamide.

Preferred compounds include those in which R⁶¹ and R⁶² are each independently hydrogen, alkyl, halo, cyano, cyanomethyl, acetyl or cycloalkyl, or together form
 5 alkylene;

R⁶⁵, R⁶⁶ and R⁶⁷ are each independently selected as in (i) or (ii):

(i) R⁶⁶ is hydrogen, unsubstituted alkyl, hydroxy, unsubstituted alkoxy, C(O)R⁴¹, carbamoyloxy or alkoxy-carbonyloxy, and

R⁶⁵ and R⁶⁷ are each independently selected from hydrogen,
 10 unsubstituted alkyl, hydroxy, C(O)R⁴¹, carbamoyloxy or alkoxy-carbonyloxy; or
 (ii) if at least one of R⁶¹ and R⁶² is not hydrogen, then any two may form methylenedioxy, and the other is selected as in (i);

x is 0 or 1; n is 2; R⁴¹ is alkyl, cycloalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylsulfonylamino or arylsulfonylamino; and R⁴³ is hydroxy or alkoxy

15 In particular, compounds which are preferred are those in which Ar¹ is 4-chloro-3-methyl-5-isoxazolyl; R⁶¹ and R⁶² are each independently hydrogen, methyl, cyclopropyl, fluoro, chloro, cyano, cyanomethyl or acetyl, or together form butylene;

R⁶⁵, R⁶⁶ and R⁶⁷ are each independently selected from (i) or (ii):

(i) R⁶⁶ is selected from hydrogen, methyl, hydroxy, methoxy, acetyl,
 20 carbamoyloxy and methoxycarbonyloxy, and

R⁶⁵ and R⁶⁷ are each independently hydrogen, methyl, hydroxy, acetyl, carbamoyloxy and methoxycarbonyloxy; or

(ii) if at least one of R⁶¹ and R⁶² is not hydrogen, then R⁶⁶ and R⁶⁷ may form methylenedioxy and R⁶⁵ is selected as in (i); and

25 R⁴⁵ is acetyl, propanoyl, 2-methylpropanoyl, cyclopropylcarbonyl, benzoyl, cyclohexylcarbonyl, methyl, 1-hydroxy-1-ethyl, hydroxymethyl, methoxyacetyl, fluoroacetyl, carboxyacetyl, hydroxyacetyl, oximinoacetyl or SO₂R⁴¹.

Particularly preferred compounds of this embodiment are selected from the following: N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-

30 isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide, N-(2-benzoyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-hydroxyethanimidoyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-propionylphenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-

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- isoxazolyl)amino)sulfonyl)-N-(2-isobutyryl-4,6-dimethylphenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclohexylcarbonyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclopropylcarbonyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide, 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thienyl)carbonyl)amino)-2,4,6-trimethylphenyl carbamate, 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thienyl)carbonyl)amino)-2,4,6-trimethylphenyl methyl carbonate, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-methoxy-2,4,6-trimethylphenyl)acetyl)-3-thiophenesulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-hydroxy-2,4,6-trimethylphenyl)acetyl)-3-
- 10 thiophenesulfonamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-1-methylethyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-ethyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2,6-diacetyl)-4-methylphenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-
- 15 isoxazolyl)amino)sulfonyl)-N-(2-(2-methoxyacetyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide, 3-(2-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thienyl)carbonyl)amino)-3,5-dimethylphenyl)-3-oxopropanoic acid, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-glycolyl-4,6-dimethylphenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-
- 20 dimethyl-6-methylsulfonyl)phenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((methylamino)sulfonyl)phenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((dimethylamino)sulfonyl)phenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((methylsulfonyl)amino)carbonyl)-
- 25 phenyl)-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-fluoroacetyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide, N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide, N-(2-benzoyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-
- 30 isoxazolyl)amino)sulfonyl)-N-(2-hydroxyethanimidoyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-propionylphenyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-isobutyryl-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-

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- (cyclohexylcarbonyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclopropylcarbonyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide, 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(5-methylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl
- 5 carbamate, 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(5-methylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl methyl carbonate, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-methoxy-2,4,6-trimethylphenyl)acetyl)-5-methyl-3-thiophenesulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-hydroxy-2,4,6-trimethylphenyl)acetyl)-5-methyl-3-thiophenesulfonamide, 3-(((4-chloro-3-methyl-5-
- 10 isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-1-methylethyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-ethyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2,6-diacetyl)-4-methylphenyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-
- 15 methoxyacetyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide, 3-(2-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(5-methylthienyl))carbonyl)amino)-3,5-dimethylphenyl)-3-oxopropanoic acid, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-glycolyl-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-methylsulfonyl)phenyl)-5-methyl-
- 20 2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((methylamino)sulfonyl)phenyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((dimethylamino)sulfonyl)phenyl)-5-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-(((methylsulfonyl)amino)carbonyl)phenyl)-5-
- 25 methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-fluoroacetyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide, N-(6-acetyl-4-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide, N-(4-acetyl-6-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide, N-(2-
- 30 acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4-methyl-2-thiophenecarboxamide, N-(2-benzoyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-hydroxyethanimidoyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-

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- dimethyl-6-propionylphenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-isobutyryl-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclohexylcarbonyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclopropylcarbonyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide, 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4-methylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl carbamate, 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4-methylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl methyl carbonate, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-methoxy-2,4,6-trimethylphenyl)acetyl)-4-methyl-3-thiophenesulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-hydroxy-2,4,6-trimethylphenyl)acetyl)-4-methyl-3-thiophenesulfonamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-1-methylethyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-ethyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2,6-diacetyl)-4-methylphenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-methoxyacetyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide, 3-(2-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4-methylthienyl))carbonyl)amino)-3,5-dimethylphenyl)-3-oxopropanoic acid, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-glycolyl-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-methylsulfonyl)phenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((methylamino)sulfonyl)phenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((dimethylamino)sulfonyl)phenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-(((methylsulfonyl)amino)carbonyl)phenyl)-4-methyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-fluoroacetyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide, N-(6-acetyl-4-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4-methyl-2-thiophenecarboxamide, N-(4-acetyl-6-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4-methyl-2-thiophenecarboxamide, N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4,5-dimethyl-2-thiophenecarboxamide, N-(2-benzoyl-4,6-dimethylphenyl)-3-(((4-chloro-3-

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- methyl-5-isoxazolyl)amino)sulfonyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-hydroxyethanimidoyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-propionylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-isobutyryl-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclohexylcarbonyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclopropylcarbonyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4,5-dimethylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl carbamate, 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4,5-dimethylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl methyl carbonate, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-methoxy-2,4,6-trimethylphenyl)acetyl)-4,5-dimethyl-3-thiophenesulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-hydroxy-2,4,6-trimethylphenyl)acetyl)-4,5-dimethyl-3-thiophenesulfonamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-1-methylethyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-ethyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2,6-diacetyl)-4-methylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-methoxyacetyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(2-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4,5-dimethylthienyl))carbonyl)-amino)-3,5-dimethylphenyl)-3-oxopropanoic acid, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-glycolyl-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-methylsulfonyl)phenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((methylamino)sulfonyl)phenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((dimethylamino)sulfonyl)phenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-(((methylsulfonyl)amino)carbonyl)phenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-fluoroacetyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide, N-(6-acetyl-4-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4,5-dimethyl-2-

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thiophenecarboxamide, and N-(4-acetyl-6-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4,5-dimethyl-2-thiophenecarboxamide.

Also among the preferred compounds are those selected from the following:

N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-cyclopropyl-2-thiophenecarboxamide, 5-acetyl-(N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide, N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-cyano-2-thiophenecarboxamide, N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-(cyanomethyl)-2-thiophenecarboxamide, N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-fluoro-2-thiophenecarboxamide, N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-chloro-2-thiophenecarboxamide, and N-2-acetyl-4,6-dimethylphenyl)-5-chloro-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4,5,6,7-tetrahydro-1-benzothiophene-2-carboxamide.

Preferred compounds are also those where W is O or CH₂. The sulfonamides are thus 2-phenoxyacetyl-3-sulfonamide, 3-phenoxyacetyl-2-sulfonamide, 2-phenylacetyl-3-sulfonamide and 3-phenylacetyl-2-sulfonamide derivatives of the above compounds.

Table 6 sets forth exemplary compounds of this embodiment and demonstrates that the compounds have activity as endothelin receptor antagonists. More preferred compounds of Table 6 are those that have the highest activities, and preferred substituents are those on the compounds with the highest activities. The data in Table 6 is intended for exemplary and comparison purposes only and is not intended to limit the scope of this embodiment in any way.

In the above embodiments, the alkyl, alkynyl and alkenyl portions are straight or branched chains, acyclic or cyclic, and have from about 1 up to about 10 carbons; in certain of the more preferred embodiments they have from 1-6 carbons, and they can have fewer than 6 carbons. The aryl, homocyclic and heterocyclic groups can have from 3 to 16, generally, 3-7, more often 5-7 members in the rings, and may be single or fused rings. The ring size and carbon chain length are selected such that the resulting molecule binds to exhibits activity as an endothelin antagonist or agonist as evidenced by in vitro or in vivo tests, particularly the tests exemplified herein.

In any of the above preferred embodiments: R¹ and R² are preferably selected independently from alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, halide,

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pseudohalide and H. In certain embodiments, R² is not halide or pseudohalide or higher alkyl.

In all embodiments, R¹ is preferably halide or lower alkyl, most preferably Br, and the compounds are, with reference to formulae IV, 2- or 3-sulfonamides, particularly thiophene sulfonamides.

TABLE 6

	COMPOUND	ET _A (μM)*	ET _B (μM)*
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-bromothiophene-2-sulfonamide	0.314	2.26
10	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(2'-thienyl)thiophene-2-sulfonamide	5.1	0.363
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-phenoxythiophene-2-sulfonamide	0.103	3.46
15	N-(3,4-dimethyl-5-isoxazolyl)benzofuran-2-sulfonamide	5.22	38.4
	N-(3,4-dimethyl-5-isoxazolyl)furan-2-sulfonamide	3.13	—
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-phenylfuran-2-sulfonamide	0.857	2.43
20	N-(4-bromo-3-methyl-5-isoxazolyl)furan-2-sulfonamide	0.75	88.1
	N-(4-bromo-3-methyl-5-isoxazolyl)-2,5-dimethylfuran-3-sulfonamide	0.46	36.5
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(phenthio)furan-2-sulfonamide	5.0	7.0
25	N-(4-Bromo-3-methyl-5-isoxazolyl)-1-(phenyl)pyrrole-2-sulfonamide	18.1	8.7
	N-(4-Bromo-3-methyl-5-isoxazolyl)-1-(4'-isopropylphenyl)pyrrole-2-sulfonamide	11.4	0.166
30	N-(4-Bromo-3-methyl-5-isoxazolyl) 1-(4'-isopropylphenyl)pyrrole-3-sulfonamide	0.838	0.211
	(4-bromo-3-methyl-5-isoxazolyl)-1-(4'-biphenyl)pyrrole-2-sulfonamide	9.17	7.84
	N-(4-bromo-3-methyl-5-isoxazolyl)2-thiophenesulfonamide	0.095 ± 0.07	27.7 ± 15.0
35	N-(4-bromo-5-methyl-3-isoxazolyl)thiophene-2-sulfonamide	0.211	27.3

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	N-(4-bromo-3-methyl-5-isoxazolyl)thiophene-3-sulfonamide	0.135	23.4
	5-(3-isoxazolyl)-N-(3-methyl-5-isoxazolyl)-2-thiophenesulfonamide	5.6	6.7
5	N-(4-Bromo-3-methyl-5-isoxazolyl)-5-(2-pyridyl)thiophene-2-sulfonamide	3.84	2.70
	N-(4-Bromo-3-methyl-5-isoxazolyl)-4,5-dibromothiophene-2-sulfonamide	0.281	2.58
10	N-(4-Bromo-3-methyl-5-isoxazolyl)-5-chloro-3-methylbenzo[b]thiophene-2-sulfonamide	0.96	1.63
	N-(4-Bromo-3-methyl-5-isoxazolyl)-5-(4-chlorobenzamidomethyl)thiophene-2-sulfonamide	0.311	2.57
	N-(4-Bromo-3-methyl-5-isoxazolyl)-4-benzenesulfonylthiophene-2-sulfonamide	0.383	--
15	4-bromo-5-chloro-N-(4-Bromo-3-methyl-5-isoxazolyl)-thiophene-2-sulfonamide	0.359	2.67
	N-(4-Bromo-3-methyl-5-isoxazolyl)-2,5-dimethylthiophene-3-sulfonamide	0.0956	7.8
20	N-(4-Bromo-3-methyl-5-isoxazolyl)-4,5-dichlorothiophene-2-sulfonamide	~0.45	~4.9
	N-(4-Bromo-3-methyl-5-isoxazolyl)-4-bromo-2,5-dichlorothiophene-3-sulfonamide	~0.28	10.4
	N-(4-Bromo-3-methyl-5-isoxazolyl)-2,5-dichlorothiophene-3-sulfonamide	~0.39	2.62
25	N-(4-Bromo-3-methyl-5-isoxazolyl)-5-{3-[1-methyl-5-(trifluoromethyl)pyrazolyl]}thiophene-2-sulfonamide	~6.7	~0.36
	N-(4-Bromo-3-methyl-5-isoxazolyl)-5-benzenesulfonylthiophene-2-sulfonamide	0.570	0.333
30	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(carbomethoxy)thiophene-3-sulfonamide	0.0208	98.1
	N-(3,4-dimethyl-5-isoxazolyl-5-phenylthiophen-2-sulfonamide	2.55	1.29
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(N-phenylaminocarbonyl)thiophene-3-sulfonamide	0.0054	18.8
35	N-(4-bromo-5-methyl-3-isoxazolyl)-2-(N-phenylaminocarbonyl)thiophene-3-sulfonamide	--	--

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(N-phenylaminocarbonyl)thiophene-3-sulfonamide	--	--
	N-(3,4-dimethyl-5-isoxazolyl)-2-(carboxyl)thiophene-3-sulfonamide	2.64	> ~100
5	N-(3,4-dimethyl-5-isoxazolyl)-2-(N-phenylaminocarbonyl)thiophene-3-sulfonamide	0.0182	~170
	N-(3,4-dimethyl-5-isoxazolyl)-2-(carbomethoxy)thiophene-3-sulfonamide	0.367	--
10	N-(4-Bromo-3-methyl-5-isoxazolyl)-2-(carboxyl)thiophene-3-sulfonamide	~0.6	~67
	N-(4-Bromo-3-methyl-5-isoxazolyl)-2-[N-(4-methoxyphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.002	2.12
15	N-(4-Bromo-3-methyl-5-isoxazolyl)-2-[N-(3-methoxyphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.003	5.86
	N-(4-Bromo-3-methyl-5-isoxazolyl)-2-[N-(2-methoxyphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.0116	13.2
20	N-(4-Bromo-3-methyl-5-isoxazolyl)-2-(N-benzylaminocarbonyl)thiophene-3-sulfonamide	0.013	12.7
	N-(4-Bromo-3-methyl-5-isoxazolyl)-2-[N-(4-ethylphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.0016	0.849
25	N-(4-Bromo-3-methyl-5-isoxazolyl)-2-[N-(4-biphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.0376	0.912
	N-(3,4-dimethyl-5-isoxazolyl)-3-methoxythiophene-2-sulfonamide	2.5	45.5
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4-ethylphenyl)thiophene-2-sulfonamide	3.23	0.0855
30	N-(4-bromo-3-methyl-5-isoxazolyl)-3-phenylthiophene-2-sulfonamide	0.0547	11.1
	N-(4-bromo-3-methyl-5-isoxazolyl)-4-phenylthiophene-2-sulfonamide	0.224	1.17
35	N-(3,4-dimethyl-5-isoxazolyl)benzo[b]thiophene-2-sulfonamide	7.22	11.1
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4'-isopropylphenyl)thiophene-2-sulfonamide	01.6	0.3

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	822N-(4-bromo-3-methyl-5-isoxazolyl)-4-(4'-isopropylphenyl)thiophene-2-sulfonamide	5.5	1.3
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4'-propylphenyl)thiophene-2-sulfonamide	5.6	0.51
5	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(4-tolulyl-aminocarbonyl)thiophene-3-sulfonamide	<0.01**	1.67**
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-isopropylphenyl)aminocarbonyl]thiophene-3-sulfonamide	<0.01**	1.13**
10	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(4-t-butylphenyl)aminocarbonylthiophene-3-sulfonamide	0.011**	2.82**
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(4-butylphenyl)aminocarbonylthiophene-3-sulfonamide	0.044**	2.84**
15	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[N-(4-sec-butylphenyl)aminocarbonyl]thiophene-3-sulfonamide	~0.008**	1.76**
	N-(3,4-dimethyl-5-isoxazolyl)-2-methylbenzo[b]thiophene-3-sulfonamide	0.167	16.6
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-methylbenzo[b]thiophene-3-sulfonamide	0.0486	3.5
20	N-(4-bromo-3-methyl-5-isoxazolyl)-2-ethylbenzo[b]thiophene-3-sulfonamide	0.0067	5.13
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-n-benzylbenzo[b]thiophene-3-sulfonamide	0.0182	~1
25	N-(4-bromo-3-methyl-5-isoxazolyl)-2-butylbenzo[b]thiophene-3-sulfonamide	0.0226	~3
	N-(4-bromo-3-methyl-5-isoxazolyl)-2- <i>i</i> -propylbenzo[b]thiophene-3-sulfonamide	0.005 0.03 [†]	5.7 10.7 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-n-propylbenzo[b]thiophene-3-sulfonamide	0.024 0.074 [†]	7.95 16.6 [†]
30	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(4-ethylbenzyl)benzo[b]thiophene-3-sulfonamide	0.048 [†]	1.1 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)benzyl]benzo[b]thiophene-3-sulfonamide	0.0015 ± 0.0014 0.0074 ± 0.0011 [†]	0.324 ± 0.78 0.939 ± 0.262 [†]
35	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(3,4,5-trimethoxybenzyl)-benzo[b]-thiophene-3-sulfonamide	0.013 [†]	1.2 [†]

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	COMPOUND	ET _A (μM) [†]	ET _B (μM) [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-ethyl-5-methylbenzo[b]thiophene-3-sulfonamide	1.89 ± 0.431 [†]	54.3 ± 2.6 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)benzyl]benzo[b]thiophene-3-sulfonamide	0.011 ± 0.005 [†]	0.936 ± 0.095 [†]
5	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(3,4-dimethoxybenzyl)benzo[b]thiophene-3-sulfonamide	0.021 ± 0.017 [†]	2.94 ± 1.32 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(benzo[b]thien-2-yl)thiophene-2-sulfonamide	16 [†]	0.80 [†]
10	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(4-methoxybenzyl)benzo[b]thiophene-3-sulfonamide	0.051 [†]	1.5 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(2-methoxybenzyl)-benzo[b]thiophene-3-sulfonamide	0.19 [†]	2.2 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-(4-chlorobenzyl)benzo[b]thiophene-3-sulfonamide	0.21 [†]	4.7 [†]
15	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(4-dimethylaminobenzyl)benzo[b]thiophene-3-sulfonamide	0.041 [†] 0.014	1.3 [†] 0.477
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-ethylbenzo[b]furan-3-sulfonamide	0.15 [†]	22 [†]
20	N-(4-chloro-3-methyl-5-isoxazolyl)-2-phenylbenzo[b]thiophene sulfonamide	0.932 [†]	46.8 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-6-methoxy-2-[3,4-(methylenedioxy)benzyl]benzo[b]thiophene-3-sulfonamide	~2 ^{est†}	2.39 [†]
25	N-(4-chloro-5-methyl-3-isoxazolyl)-2-[3,4-(methylenedioxy)benzyl]benzo[b]thiophene-3-sulfonamide	0.0055 [†]	0.364 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-methoxycarbonylthiophene-3-sulfonamide	0.631	53.2
30	N-(4-bromo-3-methyl-5-isoxazolyl)-4-(4-propylphenyl)thiophene-2-sulfonamide	0.962 [†]	0.435 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(phenylthio)thiophene-2-sulfonamide	0.0801 [†]	3.68 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-3-(phenylaminocarbonyl)thiophene-2-sulfonamide	0.163	> 100
35	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4-tolyl)amino-carbonyl]thiophene-3-sulfonamide	0.00116 0.0105 [†]	2.93 14 [†]

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
5	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4-methoxyphenyl)thiophene-2-sulfonamide	8.69 26.3 [†]	0.363 2.4 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(3-methoxyphenyl)thiophene-2-sulfonamide	3.26 23.4 [†]	0.776 4.7 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(3-thienyl)thiophene-2-sulfonamide	4.49	0.380
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-methylthiophene-2-sulfonamide	0.651	7.15
10	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(phenethyl)thiophene-2-sulfonamide	0.16 0.676 [†]	10.77 37.2 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-4-(phenethyl)thiophene-2-sulfonamide	6.64	3.97
15	N-(3,4-dimethyl-5-isoxazolyl)-2-[(4-methylphenyl)-aminocarbonyl]thiophene-3-sulfonamide	0.00336	11.3
	N-(4-bromo-3-methyl-5-isoxazolyl)-2,5-dimethyl-4-phenylthiophene-3-sulfonamide	1.40	~100
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(methyl)phenylaminocarbonyl]thiophene-3-sulfonamide	0.188	16.0
20	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(α-hydroxybenzyl)thiophene-3-sulfonamide	0.337	9.37
	N-(4-bromo-5-methyl-3-isoxazolyl)-5-(4-methylphenyl)thiophene-2-sulfonamide	7.10 15.8 [†]	0.3593 0.25 [†]
25	N-(4-bromo-3-methyl-5-isoxazolyl)-5-phenylthiophene-2-sulfonamide	3.53 36.6 [†]	0.417 2.4 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-[4-(trifluoromethyl)phenyl]thiophene-2-sulfonamide	6.39 6.31 [†]	0.0835 .282 [†]
30	N,N'-bis{3-[(4-bromo-3-methyl-5-isoxazolyl)aminosulfonyl]thien-2-yl} urea	0.0692 0.295 [†]	0.290 1.19 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(hydroxymethyl)thiophene-3-sulfonamide	0.160 1.55 [†]	44.1 --
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(2-formylphenyl)thiophene-3-sulfonamide	3.46 12.31 [†]	0.529 1.28 ± 0.71 [†]
35	N,N'-bis{3-[3,4-dimethyl-5-isoxazolyl)aminosulfonyl]thien-2-yl}urea	1.01 ± 1.03 2.7 [†]	3.7 ± 2.7 5.9 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-[(3-methoxyanilino)methyl]thiophene-3-sulfonamide	0.214 0.933 [†]	5.34 7.7 [†]

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	COMPOUND	ET _A (μM) [*]	ET _B (μM) [*]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(3-aminophenyl)thiophene-2-sulfonamide	0.537 1.44 [†]	1.07 2.63 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-[3,5-bis(trifluoromethyl)phenyl]thiophene-2-sulfonamide	0.794 5.9 [†]	12.0 15.5 [†]
5	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(3,3-dimethylbutyn-1-yl)thiophene-2-sulfonamide	1.12 7.24 [†]	24.0 35.5 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(2-methoxyphenyl)thiophene-2-sulfonamide	0.381	1.097
10	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(2-tolyl)thiophene-2-sulfonamide	0.432	0.313
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3-carboxyphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.062 [†]	> 100 [†]
15	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[2-carboxyphenyl]aminocarbonyl]thiophene-3-sulfonamide	0.21 [†]	20 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(aminocarbonyl)thiophene-3-sulfonamide	0.84 [†]	> 100 [†]
20	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(5-dimethylamino-1-naphthyl)sulfonylaminocarbonyl]thiophene-3-sulfonamide	0.97 [†]	3.9 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(5-methyl-2-thienyl)thiophene-2-sulfonamide	17 [†]	0.21 [†]
25	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxyphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.017 [†]	9.8 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)phenoxy]carbonyl]thiophene-3-sulfonamide	0.0073 [†]	6.0 [†]
30	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[(3,4-methylenedioxy)phenyl]thiophene-2-sulfonamide	0.50 [†]	79 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[(3,4-methylenedioxy)benzyl]thiophene-2-sulfonamide	8.1 [†]	3.2 [†]
35	N-(4-bromo-3-methyl-5-isoxazolyl)-3-benzylthiophene-2-sulfonamide	1.6 [†]	39 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(3-tolyl)thiophene-2-sulfonamide	15 [†]	4.2 [†]

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	COMPOUND	ET _A (μM) [†]	ET _B (μM) [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)benzyl]thiophene-3-sulfonamide	0.27 [†]	7.7 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)benzoyl]thiophene-3-sulfonamide	2.0 [†]	15 [†]
5	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(2-hydroxyphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.013 [†]	38 [†]
10	N-(3,4-dimethyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)phenoxy carbonyl]thiophene-3-sulfonamide	6.1 [†]	> ~50 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(5-ethylthien-2-yl)thiophene-2-sulfonamide	24 [†]	7.7 [†]
15	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)benzoyl]aminocarbonyl]thiophene-3-sulfonamide	0.089 [†]	37 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)phenoxy carbonyl]thiophene-3-sulfonamide	0.0065 [†]	7.4 [†]
20	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(1-pentynyl)thiophene-2-sulfonamide	29 [†]	5.6 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-5-(5-ethylthien-2-yl)thiophene-2-sulfonamide	12 [†]	0.71 [†]
25	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)phenylacetyl]thiophene-3-sulfonamide	0.0091 [†]	5.5 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)phenoxy carbonylamino]thiophene-3-sulfonamide	0.087 [†]	5.9 [†]
30	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(2-chloro-3,4-methylenedioxy)phenoxy methyl]thiophene-3-sulfonamide	13 [†]	0.76 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[<i>trans</i> -[3,4-methylenedioxy]cinnamyl]thiophene-3-sulfonamide	0.14 [†]	1.4 [†]
35	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(1-naphthyl)thiophene-2-sulfonamide	14 [†]	1.4 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(3-nitrophenyl)thiophene-2-sulfonamide	26 [†]	4.5 [†]

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	COMPOUND	ET _A (μM) [†]	ET _B (μM) [†]
5	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)phenylureido]thiophene-3-sulfonamide	0.57 [†]	1.3 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)phenylacetyl]thiophene-3-sulfonamide	0.021 [†]	6.5 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4-methoxycarbonylphenyl)thiophene-2-sulfonamide	> 100 [†]	17 [†]
10	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4-carboxyphenyl)thiophene-2-sulfonamide	> 100 [†]	31 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(4-tolyl)aminocarbonylthiophene-2-sulfonamide	28 [†]	8.6 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(2-methylfuranyl)thiophene-2-sulfonamide	32 [†]	7.5 [†]
15	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)benzyloxycarbonyl]thiophene-3-sulfonamide	.42 [†]	12 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-(3,4-methylenedioxyphenyl)]ethoxycarbonyl-3-sulfonamide	.23 [†]	6.2 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-{[4-(3,4-methylenedioxybenzyl)piperazin-1-yl]carbonyl}thiophene-3-sulfonamide	20 [†]	> ~ 100 [†]
20	N-(4-chloro-3-methyl-5-isoxazolyl)-2-aminothiophene-3-sulfonamide	14 [†]	6.2 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-5-(benzyloxymethyl)thiophene-2-sulfonamide	12 [†]	9.0 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-{1-cyano-1-[(3,4-methylenedioxy)phenyl]acetyl}thiophene-3-sulfonamide	2.1 [†]	27 [†]
25	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)phenethyl]thiophene-3-sulfonamide	0.21 [†]	9.2 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(3-dimethylamino)phenoxy]carbonylthiophene-3-sulfonamide	1.4 [†]	60 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-1-methylindole-2-sulfonamide	77 [†]	~100 [†]

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	COMPOUND	ET _A (μM) [†]	ET _B (μM) [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(cyclohexyloxycarbonyl)thiophene-3-sulfonamide	0.44 [†]	34 [†]
5	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[β-hydroxy(3,4-methylenedioxy)phenylethyl]thiophene-3-sulfonamide	0.053 [†]	16 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-carboxyl-1-methylindole-3-sulfonamide	0.59 [†]	104 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4-oxacyclohexyl)oxycarbonyl]thiophene-3-sulfonamide	1.37 [†]	—
10	N-2-[3,4-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide	1.8 [†]	32.5 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4-tolyl)aminocarbonyl]-1-methylindole-3-sulfonamide	31.3 [†]	14.7 [†]
15	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4-methoxyphenoxy)carbonyl]thiophene-3-sulfonamide	0.023 [†]	15 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-1-[3,4-(methylenedioxy)benzyl]indole-2-sulfonamide	5.29 [†]	18.6 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(4-methylphenoxy)carbonyl]thiophene-3-sulfonamide	122 [†]	9.7 [†]
20	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4-methoxyphenyl)acetyl]thiophene-3-sulfonamide	0.043 [†]	10.1 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[(4-methylphenoxy)methyl]thiophene-2-sulfonamide	1.64 [†]	22.8 [†]
25	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(4-methylphenoxy)methyl]thiophene-3-sulfonamide	1.2 [†]	15 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4-methyl- <i>trans</i> -styryl)thiophene-2-sulfonamide	0.94 [†]	0.66 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4-methylphenethyl)thiophene-2-sulfonamide	0.347 [†]	9.4 [†]
30	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(4-methylphenyl)acetyl]thiophene-3-sulfonamide	0.198 [†]	9.13 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3-methoxyphenyl)acetyl]thiophene-3-sulfonamide	0.030 [†]	19.1 [†]
35	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4-methylphenethyl)-5-(4-tolyl)thiophene-2-sulfonamide	6.1 [†]	2.09 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4-methylbenzyl)-5-(4-tolyl)thiophene-2-sulfonamide	4.69 [†]	1.56 [†]

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	COMPOUND	ET _A (μM) [*]	ET _B (μM) [*]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4-methyl- <i>trans</i> -styryl)-5-(4-tolyl)thiophene-2-sulfonamide	6.9 [†]	1.58 [†]
5	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[β,β-(ethylene-dioxy)-3,4-(methylenedioxy)phenethyl]thiophene-3-sulfonamide	0.128 [†]	2.09 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[β-(dimethyl-amino)-3,4-(methylenedioxy)phenethyl]thiophene-3-sulfonamide	20.9 [†]	~100 [†]
10	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[α-hydroxy-[3,4-(methylenedioxy)phenyl]acetyl]thiophene-3-sulfonamide	2.5 [†]	30 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(5-methyl-3-isoxazolyl)aminocarbonyl]thiophene-3-sulfonamide	0.066 [†]	92 [†]
15	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3-hydroxyl-6-pyridazinyl)aminocarbonyl]thiophene-3-sulfonamide	0.066 [†]	81.3 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-acetyl-4,5-(methylenedioxy)phenyl]aminocarbonyl]thiophene-3-sulfonamide	0.010 [†]	31.6 [†]
20	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[(3,4-(methylenedioxy)phenoxy)methyl]thiophene-2-sulfonamide	0.513 [†]	9.6 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(4-methyl)(cinnamyl)]thiophene-3-sulfonamide	0.26 [†]	0.413 [†]
25	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4,5-dimethoxy-2-methoxycarbonylphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.55 [†]	--
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2-methyl-1,3,4-thiadiazol-5-yl)aminocarbonyl]thiophene-3-sulfonamide	0.13 [†]	--
30	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4,5-dimethoxy-2,4,5-dimethoxy-2-methoxycarbonyl)phenyl]phenylaminocarbonyl]thiophene-3-sulfonamide	3.80 [†]	--
35	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2-carboxyl-4,5-(methylenedioxy)phenyl)aminocarbonyl]thiophene-3-sulfonamide	1.43 [†]	--
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[3,4-(methylenedioxy)phenethyl]thiophene-2-sulfonamide	0.236 [†]	18 [†]

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	COMPOUND	ET _A (μM) [*]	ET _B (μM) [*]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[3,4-(methylenedioxy)- <i>trans</i> -styryl]thiophene-2-sulfonamide	0.218 [†]	10 [†]
5	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(4-methyl)phenethyl]thiophene-3-sulfonamide	0.106 [†]	40.1 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-{[2-acetyl-4,5-(methylenedioxy)phenyl]aminocarbonyl}thiophene-3-sulfonamide	0.032 [†]	—
10	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[4-methoxy-2-methylphenyl]aminocarbonyl]thiophene-3-sulfonamide	0.027 [†]	0.14 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2-cyano-4,5-dimethoxyphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.0039 [†]	12.2 [†]
15	N-(3,4-dimethyl-5-isoxazolyl)-2-(4-tolylacetylphenyl)thiophene-3-sulfonamide	.0027 [†]	29.2 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide	0.0273 [†]	12.2 [†]
20	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2,4-dimethoxyphenyl)aminocarbonyl]thiophene-3-sulfonamide	0.158 [†]	63.1 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(3-methyl-6-pyridyl)aminocarbonyl]thiophene-3-sulfonamide	0.023 [†]	43.7 [†]
25	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-hydroxy-4-methylphenyl]aminocarbonyl]thiophene-3-sulfonamide	.006 [†]	—
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2-cyano-4,5-(methylenedioxy)phenyl]aminocarbonyl]thiophene-3-sulfonamide	0.0034 [†]	40.4 [†]
30	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylaminocarbonyl]thiophene-3-sulfonamide	0.0030 [†]	355 [†]
35	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-carboxamido-4,5-dimethoxyphenylamino-carbonyl)thiophene-3-sulfonamide	0.011 [†]	61 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-(2,4-dimethylphenylacetyl)thiophene-3-sulfonamide	0.0027 [†]	17.4 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,4-dimethylphenylacetyl)thiophene-3-sulfonamide	0.0004 [†]	4.8 [†]

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(2,4-dimethylphenylacetyl)thiophene-3-sulfonamide	0.0008 ^{†**}	3.6 [†]
5	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)]phenylaminocarbonyl-3-thiophenesulfonamide	0.0073 [†]	9.2 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide	0.0032 [†]	9 [†]
10	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-(2-acetoxyethyl)phenylaminocarbonyl]thiophene-3-sulfonamide	0.0045 [†]	25.7 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-(2-hydroxyethyl)phenylaminocarbonyl]thiophene-3-sulfonamide	0.0056 [†]	16.8 [†]
15	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3,5-dimethylphenylacetyl)thiophene-3-sulfonamide	0.045 [†]	17.7 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,5-dimethylphenylacetyl)thiophene-3-sulfonamide	0.007 [†]	18 [†]
20	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methanesulfonylaminomethyl]-4,5-(methylenedioxy)phenylaminocarbonyl]thiophene-3-sulfonamide	0.0068 [†]	19.8 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-cyanomethyl-4,5-(methylenedioxy)-6-cyanomethyl]phenylaminocarbonyl-3-thiophenesulfonamide	0.0038 [†]	25 [†]
25	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-hydroxypropyl-4,5-(methylenedioxy)phenylaminocarbonyl]thiophene-3-sulfonamide	0.0073 [†]	8.3 [†]
30	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[2-methyl-4,5-(methylenedioxy)cinnamyl]thiophene-2-sulfonamide	~0.1 ^{***}	~6 ^{***}
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[2-methyl-4,5-(methylenedioxy)phenethyl]thiophene-2-sulfonamide	~0.1 ^{***}	~5 ^{***}
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[[2-propyl-4,5-(methylenedioxy)phenoxy]methyl]thiophene-2-sulfonamide	~0.2 ^{***}	~1.5 ^{***}
35	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-(2-acetoxyethoxy)]phenylaminocarbonyl]thiophene-3-sulfonamide	~0.02 ^{***}	~18 [†]

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	COMPOUND	ET _A (μM) [*]	ET _B (μM) [*]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-(2-hydroxyethoxy)phenylaminocarbonyl]thiophene-3-sulfonamide	~0.01 [†] ***	~18 [†]
5	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-cyano-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide	~0.3 [†] ***	~0.7 [†]
10	N-(4-chloro-3-methyl-5-isoxazolyl)-2-{2-[(dimethylamino)carbonylmethyl]-4,5-(methylenedioxy)phenylaminocarbonyl}thiophene-3-sulfonamide	0.009 [†]	13.8 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylhydroxyimino]thiophene-3-sulfonamide	0.794 [†]	6.49 [†]
15	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenethyl]thiophene-3-sulfonamide	0.0619 [†]	8.90 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[2-(hydroxymethyl)-4,5-(methylenedioxy)cinnamyl]thiophene-2-sulfonamide	0.0795 [†]	3.24 [†]
20	N-(4-bromo-3-methyl-5-isoxazolyl)-3-{2-[(tetrahydro-4H-pyran-2-ylxoy)methyl]-4,5-(methylenedioxy)cinnamyl}thiophene-2-sulfonamide	0.0967 [†]	4.14
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(2,4-dimethylphenethyl)thiophene-2-sulfonamide	0.1006 [†]	4.30 [†]
25	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(2,4-dimethylcinnamyl)thiophene-2-sulfonamide	0.180 [†]	2.97 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(2,4-dimethylcinnamyl)thiophene-3-sulfonamide	0.166 [†]	2.97 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[(2,4-dimethylphenoxy)methyl]thiophene-2-sulfonamide	0.346 [†]	7.45 [†]
30	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(2,4-dimethylphenoxy)methyl]thiophene-3-sulfonamide	0.308 [†]	4.48 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-5-(phenylaminocarbonyl)thiophene-2-sulfonamide	28.1 [†]	60.6 [†]
35	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[β-acetoxy-2-methyl-4,5-(methylenedioxy)styryl]thiophene-3-sulfonamide	0.00544	3.74 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2,3,4-trimethoxy-6-cyano)phenylaminocarbonyl]thiophene-3-sulfonamide	0.000169 [†]	12.5 [†]

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	COMPOUND	ET _A (μM) ⁺	ET _B (μM) ⁺
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-(cyano)phenyl]benzo[b]thiophene-3-sulfonamide	6.33 [†]	8.82 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)phenyl]benzo[b]thiophene-3-sulfonamide	0.550 [†]	52.6 [†]
5	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(2-tolyl)thiophene-2-sulfonamide	0.324 [†]	55.1 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(3-tolyl)thiophene-2-sulfonamide	0.832 [†]	21.2 [†]
10	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(2-tolyl)thiophene-2-sulfonamide	0.302 [†]	31% @ 100 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(3-methoxyphenyl)thiophene-2-sulfonamide	0.334 [†]	**
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(3-methoxyphenyl)thiophene-2-sulfonamide	1.32 [†]	56.3 [†]
15	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(2-methoxyphenyl)thiophene-2-sulfonamide	1.71 [†]	59.1 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4-ethylphenyl)thiophene-2-sulfonamide	0.184	43.9 [†]
20	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4-propylphenyl)thiophene-2-sulfonamide	0.0873	8.48 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4- <i>iso</i> -propylphenyl)thiophene-2-sulfonamide	0.218	28.3 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4-butylphenyl)thiophene-2-sulfonamide	0.160	6.11 [†]
25	N-(3,4-dimethyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide	0.00328 [†]	34.3 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.000626 [†]	8.27 [†]
30	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,4,6-trimethylphenylacetyl)thiophene-3-sulfonamide	0.000238 [†]	3.82 [†]
	N-(4-chloro-5-methyl-3-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide	0.000625 [†]	3.69 [†]
35	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)cinnamyl]thiophene-3-sulfonamide	0.0804 [†]	3.28 [†]

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	COMPOUND	ET _A (μM) [†]	ET _B (μM) [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(2,4-dimethylphenethyl)thiophene-3-sulfonamide	0.0555 [†]	3.48 [†]
5	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4-methoxycarbonyl-2,6-dimethyl)-phenylaminocarbonyl]thiophene-3-sulfonamide	0.000266 [†]	9.78 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(phenoxycarbonyl)thiophene-3-sulfonamide	4.41 [†]	31%@100 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(phenoxycarbonyl)thiophene-3-sulfonamide	2.71 [†]	20%@100 [†]
10	N-(3,4-dimethyl-5-isoxazolyl)-2-[(3,4-(methylenedioxy)phenoxy]carbonyl]thiophene-3-sulfonamide	3.61 [†]	30%@100 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(2-methylphenoxy)carbonyl]thiophene-3-sulfonamide	0.684 [†]	105 [†]
15	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3-methylphenoxy)carbonyl]thiophene-3-sulfonamide	1.20 [†]	111 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(2,4-dimethylphenoxy)carbonyl]thiophene-3-sulfonamide	0.291 [†]	43.2 [†]
20	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(2-methoxyphenoxy)carbonyl]thiophene-3-sulfonamide	0.761 [†]	29%@100 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3-methoxyphenoxy)carbonyl]thiophene-3-sulfonamide	1.20 [†]	90 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(4-methoxyphenoxy)carbonyl]thiophene-3-sulfonamide	1.73 [†]	111 [†]
25	N-(3,4-dimethyl-5-isoxazolyl)-2-[(4-methoxyphenoxy)carbonyl]thiophene-3-sulfonamide	0.324 [†]	68.5 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-[(4-methylphenoxy)carbonyl]thiophene-3-sulfonamide	0.324 [†]	68.5 [†]
30	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4-methylphenoxy)carbonyl]thiophene-3-sulfonamide	2.52 [†]	19%@100 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2,4-dimethylphenoxy)carbonyl]thiophene-3-sulfonamide	3.22 [†]	43%@100 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-[(2,4-dimethylphenoxy)carbonyl]thiophene-3-sulfonamide	0.648 [†]	68.5 [†]
35	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(2-propyl-4,5-(methylenedioxy)phenoxy]carbonyl]thiophene-3-sulfonamide	0.274 [†]	21%@100 [†]

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	COMPOUND	ET _A (μM) [*]	ET _B (μM) [*]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonyl-2,4,6-trimethylphenylamino-carbonyl)thiophene-3-sulfonamide	0.138 [†]	11.9 [†]
5	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(2,4-dimethylphenyl)thiophene-2-sulfonamide	0.1002 [†]	60.3 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-(phenoxy-carbonyl)thiophene-3-sulfonamide	2.85 [†]	31% [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4- <i>iso</i> -butylphenyl)thiophene-2-sulfonamide	0.0823 [†]	2.76 [†]
10	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4- <i>iso</i> -pentylphenyl)thiophene-2-sulfonamide	0.155 [†]	3.31 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-[(2,4,6-trimethylphenoxy)methyl]thiophene-2-sulfonamide	0.0457 [†]	4.68 [†]
15	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(2,4,6-trimethylphenoxy)methyl]thiophene-3-sulfonamide	0.0562 [†]	3.39 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(2,4,6-trimethylcinnamyl)thiophene-2-sulfonamide	0.0490 [†]	1.86 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(2-methyl-4-propylphenyl)thiophene-2-sulfonamide	0.0468 [†]	3.63 [†]
20	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4- <i>iso</i> -butyl-2-methylphenyl)thiophene-2-sulfonamide	0.0468 [†]	1.66 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4- <i>iso</i> -pentyl-2-methylphenyl)thiophene-2-sulfonamide	0.107 [†]	2.40 [†]
25	N-(4-bromo-3-methyl-5-isoxazolyl)-2-{[3,4-(methylenedioxy)phenoxy]methyl}thiophene-3-sulfonamide	0.302 [†]	6.61 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-{[4,5-(methylenedioxy)-2-propylphenoxy]methyl}thiophene-3-sulfonamide	0.188 [†]	0.407 [†]
30	N-(4-bromo-3-methyl-5-isoxazolyl)-2-(2,4,6-trimethylphenethyl)thiophene-3-sulfonamide	0.0417 [†]	1.23 [†]
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-(2,4,6-trimethylphenethyl)thiophene-2-sulfonamide	0.055 [†]	1.62 [†]
35	N-(3,4-dimethyl-5-isoxazolyl)-2-[(2,4,6-trimethylphenoxy)carbonyl]thiophene-3-sulfonamide	0.537 [†]	8%@100 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2,4,6-trimethylphenoxy)carbonyl]thiophene-3-sulfonamide	0.0776 [†]	30.2 [†]

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	COMPOUND	ET _A (μM) [*]	ET _B (μM) [*]
	N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(2,4,6-trimethylphenoxy)carbonyl]thiophene-3-sulfonamide	0.479 [†]	24.5 [†]
5	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide	0.01464 ±0.00624 [†]	52.782 ±23.24 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2,3,4-trimethoxy-6-cyano)phenylaminocarbonyl]thiophene-3-sulfonamide	0.00024 [†]	6.998 [†]
10	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00160 [†]	11.272 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-[(4-methoxyphenoxy)carbonyl]thiophene-3-sulfonamide	5.88 [†]	13%@100 [†]
15	N-(3,4-dimethyl-5-isoxazolyl)-2-[(4-methoxyphenoxy)carbonyl]thiophene-3-sulfonamide	2.5 [†]	33%@100 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4-methylphenoxy)carbonyl]thiophene-3-sulfonamide	3.2 [†]	43%@100 [†]
20	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.000321 [†] 0.00092 [†]	16.5 [†] --
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00118 ±0.00065 [†]	38.782 ±23.377 [†]
25	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00177 ±0.00036 [†]	106.066 ±14.632 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00086 ±0.00012 [†]	729.577 ±1094.031 [†]
30	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00067 ±0.00014 [†]	74.224 ±48.771 [†]
35	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00100 ±0.00012 [†]	114.040 ±2.599 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, trifluoroacetic acid salt	0.01337 [†]	--

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	COMPOUND	ET _A (μM) [†]	ET _B (μM) [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(α-methyl-2-methyl-4,5-(methylenedioxy)phenylacetyl)thiophene-3-sulfonamide	0.08531 [†]	--
5	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(α-carboxymethyl-2-methyl-4,5-(methylenedioxy)phenylacetyl)thiophene-3-sulfonamide	0.08110 [†]	--
10	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00162 ±0.00026 [†]	67.622 ±67.866 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-carbamoyl-4,6-dimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00146 [†]	11.885 [†]
15	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00171 ±0.00082 [†]	18.676 ±8.672 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.01191 [†]	22.387 [†]
20	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-carboxyl-4,6-dimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.02831 [†]	16.982 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-phenyl-4,6-dimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.01589 [†]	29.512 [†]
25	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00152 ±0.00036 [†]	57.231 ±17.270 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00092 ±0.00059 [†]	25.520 ±10.416 [†]
30	N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00088 ±0.00007 [†]	7.540 ±1.740 [†]
35	N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00051 ±0.00039 [†]	19.699 ±9.597 [†]
40	N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00088 [†]	3.083 [†]

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	COMPOUND	ET _A (μM) [†]	ET _B (μM) [†]
	-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00066 [†]	9.550 [†]
5	N-(3,4-dimethyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00156 ± 0.00025 [†]	22.772 ± 2.590 [†]
	N-(3,4-dimethyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00097 [†]	155.955 [†]
10	N-(3,4-dimethyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.00111 [†]	33.806 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(pentamethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.02985 [†]	30.974 [†]
15	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,4,6-trimethylbenzylaminocarbonyl)thiophene-3-sulfonamide	17,458.222 [†]	69.183 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylbenzylaminocarbonyl)thiophene-3-sulfonamide	0.5310 [†]	81.470 [†]
20	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.0006 [†]	~45 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.0015 [†]	~ > 100 [†]
25	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.0006 [†]	> > 100 [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide	0.0004 [†]	~80 [†]
30	N-(4-chloro-3-methyl-5-isoxazolyl)-2-{[3,4-(methylenedioxy)-6-methylphenyl]acetyl}-thiophene-3-sulfonamide	1.0 [§]	--
35	N-(2-acetyl-4,6-dimethylphenyl)-3-{[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl}-2-thiophenecarboxamide	18.1 [§]	--
40	N-(2-cyano-3,4,6-trimethylphenyl)-3-{[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl}-2-thiophenecarboxamide	18.6 [§]	--

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	COMPOUND	ET _A (μM) [*]	ET _B (μM) [*]
5	3-{[(4-chloro-3-methyl-5-isoxazolyl)amino] sulfonyl}-N-(3,4,6-trimethyl-2-propanoylphenyl)-2-thiophenecarboxamide	23.9 ^s	--
	3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-[2-(1-hydroxyethyl)-4,6-dimethylphenyl]-2-thiophene carboxamide	26.4 ^s	--
	3-{[(4-chloro-3-methyl-5-isoxazolyl)amino] sulfonyl}-N-{2-[(dimethylamino)carbonyl]-4,6-dimethylphenyl}-2-thiophene carboxamide	14.4 ^s	--
10	3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-{2,4-dimethyl-6-[(methyloxy)ethanimidoyl]phenyl}-2-thiophene carboxamide	23.6 ^s	--
15	3-{[(3-[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl)-2-thiophenyl]carbonyl]amino}-2,4,6-trimethylphenyl-N,N-dimethylsulfamate	0.3 ^s	--
20	3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-{3-[(cyclopropylmethyl)oxy]-2,4,6-trimethylphenyl}-2-thiophenecarboxamide	9.4 ^s	--
	3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-(2,4,6-trimethyl-5-pyrimidinyl)-2-thiophenecarboxamide	2.0 ^s	--
25	N-(2-acetyl-3,4,6-trimethylphenyl)-3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-2-thiophenecarboxamide	103.8 ^s	--
	3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-(2-cyano-3,4,6-trimethylphenyl)-2-thiophenecarboxamide	55.7 ^s	--
30	N-(2-chloro-4,6-dimethylphenyl)-3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-2-thiophenecarboxamide	20.7 ^s	--
35	3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-(4,6-diacetyl-3-hydroxy-2-propylphenyl)-2-thiophenecarboxamide	0.1 ^s	--
	3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-(2,4-dimethyl-6-[2-(methylsulfonyl)acetyl]phenyl)-2-thiophenecarboxamide	13.7 ^s	--

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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-(2,4-dimethyl-6-[[methyl(2,2-dimethylpropyl)amino]carbonyl]phenyl)-2-thiophenecarboxamide	2.7 [†]	--
5	3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-[2,4-dimethyl-6-(methylsulfonyl)phenyl]-2-thiophenecarboxamide	64.1 [‡]	--
10	3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-[2,4-dimethyl-6-(1,3-oxazol-2-yl)phenyl]-2-thiophenecarboxamide	17.9 [‡]	--
	3-[[[4-chloro-5-isoxazolyl]amino]sulfonyl]-N-[2-(2-propylsulfonyl)-4,6-dimethylphenyl]-2-thiophenecarboxamide	-- [§]	--
15	3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-[2,4-dimethyl-6-(propylsulfonyl)phenyl]-2-thiophenecarboxamide	-- [§]	--
	3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-(2-ethyl-4,6-dimethylphenyl)-2-thiophenecarboxamide	3.8 [†]	--
20	3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-[2,6-dimethyl-4-(1,3-oxazol-2-yl)phenyl]-2-thiophenecarboxamide	1.1 [†]	--

* results are generally the average of 2 to 5 experiments

25 ** preliminary results or results in which one or more data points were only determined approximately

† assay performed with incubation at 24° C. As described in the Examples, incubation at the higher temperature reduces the activity by a factor of 2- to about 10-compared to the activity at 4° C

30 -- data not available or measured as % inhibition @ 100 μM

% inhibition @ 100 μM

§ activity relative to N-(4-chloro-3-methyl-5-isoxazolyl)-2-[[3,4-(methylenedioxy)-6-methylphenyl]acetyl]-thiophene-3-sulfonamide

35 b. Ar² is a heterocycle with one heteroatom and two or more fused rings

Compounds in Ar² is a heterocycle with one heteroatom and two or more fused rings are provided. The heteroatom is O, S or N and Ar² is selected from among, but not limited to, quinolyl, isoquinolyl, dibenzofuryl, bibenzothienyl, and dibenzopyrrolyl
40 compounds and other such groups. The fused rings may be substituted with one or more substituents selected from among substituents set forth for R⁸, R⁹ and R¹⁰ above,

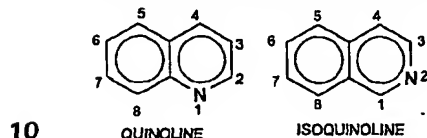
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at any position. The sulfonamide portion of the compounds may be linked at any position.

(1) Ar² is quinolyl and isoquinolyl

Presently, preferred compounds are quinolines, particularly, 8-quinolinesulfonamides.

5 The numbering scheme is as follows:



R¹ and R² are selected as described for the thienyl, furyl and pyrrolyl compounds, any of the rings may be substituted with one or more substituents selected from hydrogen or are selected as described above for R²⁶ and R¹³.

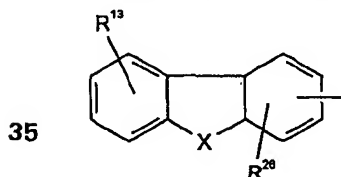
15 Exemplary quinolinesulfonamides are set forth in Table 7:

TABLE 7

	COMPOUND	ET _A (μM)	ET _B (μM)
	N-(3,4-dimethyl-5-isoxazolyl)-8-quinolinesulfonamide	53 ± 7	63 ± 4
20	N-(4-bromo-3-methyl-5-isoxazolyl)-8-quinolinesulfonamide	0.12 ± 0.0	14 ± 1
	N-(4-bromo-5-methyl-3-isoxazolyl)-8-quinolinesulfonamide	0.19 ± 0.04	12 ± 2
	N-(4-Benzyl-3-methyl-5-isoxazolyl)-8-quinolinesulfonamide	39 ± 3	63 ± 10
25	8-ethoxy-N-(4-bromo-3-methyl-5-isoxazolyl)quinoline-5-sulfonamide	1.7 ± 0.5	24 ± 0.3

(2) Ar² is dibenzofuryl, bibenzothienyl, and dibenzopyrrolyl

30 In certain embodiments Ar² is dibenzofuryl, bibenzothienyl, and dibenzopyrrolyl and has the following formula (XXIV):



35 which is unsubstituted or substituted with one or more substituents selected from R¹³ and R²⁶. In these embodiments, R¹ and R² are selected as described above for the
40 thienyl, furyl and pyrrolyl compounds. These compounds are substituted as described

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- above for the biphenyl compounds in which R^{13} and R^6 ; X is $-\text{CH}=\text{CH}-$, O, S, NR^{11} , in which R^{11} is as set forth above (compounds in which X is $-\text{CH}=\text{CH}-$ are phenanthrenesulfonamides, which are discussed above), and R^{13} and R^{26} are independently selected from H, OH, OHNH, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, dialkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, carbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms, preferably from 1 to 6 atoms, and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons, preferably 4 to 10 carbons.

- In more preferred embodiments, R^1 is halide or methyl; R^2 is selected from lower alkyl, lower alkenyl, lower alkynyl and lower haloalkyl; R^{26} and R^{13} are selected from H, lower alkyl, haloalkyl and halide. In more preferred embodiments R^1 is Cl, Br or CH_3 ; R^2 is selected from H, CH_3 , C_2H_5 , CF_3 , $n\text{-C}_3\text{H}_7$, cyclo- C_3H_7 and C_4H_9 ; and R^{26} and R^{13} are each independently selected from H, halide, NH_2 , CF_3 , CH_3 , CN, CH_3 , $(\text{CH}_3)_3\text{C}$, C_5H_{11} , CH_3O , $n\text{-C}_4\text{H}_9\text{O}$ and $\text{CH}_2=\text{CH}$. In yet more preferred embodiments, R^2 is H, CH_3 , C_2H_5 , or CF_3 ; R^{26} and R^{13} are independently selected from H, CH_3 , C_2H_5 , CF_3 , and halide; and X is O.

Exemplary compounds include those set forth in Table 8:

TABLE 8

	COMPOUND	ET_A (μM) [*]	
		ET_A (μM) [*]	ET_B (μM) [*]
25	N-(4-bromo-3-methyl-5-isoxazolyl)dibenzofuran-4-sulfonamide	0.39	10
	N-(3,4-Dimethyl-5-isoxazolyl)-3-dibenzofuransulfonamide	6.1 ± 1.2	0.81 ± 0.13
	N-(4-bromo-3-methyl-5-isoxazolyl)-3-dibenzofuransulfonamide	1.05 ± 0.05	0.23 ± 0.05
30	N-(3,4-dimethyl-5-isoxazolyl)dibenzothiophene-4-sulfonamide	0.37 ± 0.06	1.8 ± 0.4
	N-(4-bromo-3-methyl-5-isoxazolyl)dibenzothiophene-4-sulfonamide	0.115 ± 0.02	0.47 ± 0.13

- * results based on 1 to 4 experiments

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- c. Ar^2 is a six-membered heterocycle with one heteroatom selected from S, O or NR^{11}

Preferred six-membered heterocyclic rings are pyridyl rings. The pyridyl groups may be substituted with one or more substituents selected from R^{13} , R^8 and R^{26} , as defined above and may be 2-, 3- or 4-sulfonamides. R^1 and R^2 are selected as described above for the thiphenyl, furyl and pyrrolyl compounds.

Compounds in which Ar^2 is a pyridyl group include, but are limited to, N-(4-bromo-3-methyl-5-isoxazolyl)pyridine-2-sulfonamide, N-(4-bromo-5-methyl-3-isoxazolyl)pyridine-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)pyridine-2-sulfonamide, N-(4,5-dimethyl-3-isoxazolyl)pyridine-2-sulfonamide, 3-methoxycarbonyl-N-(4-bromo-5-methyl-3-isoxazolyl)pyridine-2-sulfonamide and 3-methoxycarbonyl-N-(4-bromo-5-methyl-3-isoxazolyl)pyridine-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-3-(N-phenylaminocarbonyl)pyridine-2-sulfonamide, N-(4-bromo-5-methyl-3-isoxazolyl)-3-(N-phenylaminocarbonyl)pyridine-2-sulfonamide, and N-(4-bromo-3-methyl-5-isoxazolyl)-3-(N-phenylaminocarbonyl)pyridine-2-sulfonamide. These compounds appear to be ET_A selective with IC_{50} concentrations on the order of 1-3 μM or less.

- d. Ar^2 is a heterocycle with two or more heteroatoms

Compounds in which Ar^2 is a heterocycle that contains two or more heteroatoms selected from O, S, N, and NR^{11} , including, but are not limited to pyrimidinyl, purinyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, benzofuryl, benzothienyl and benzopyrrolyl, are provided. These compounds may be unsubstituted or substituted with one or more substituents selected from those set forth for R^3 , R^8 or R^{26} . Particular compounds that have been synthesized, include:

TABLE 9

	COMPOUND	ET_A (μM)*	ET_B (μM)*
25	5-acetamido-4-methyl-N-(3,4-dimethyl-5-isoxazolyl)thiazole-2-sulfonamide	~59	36 ± 6
	5-acetamido-4-methyl-N-(4-bromo-3-methyl-5-isoxazolyl)thiazole-2-sulfonamide	6.7	14 ± 2
30	N-(3,4-dimethyl-5-isoxazolyl)-4-benzofuransulfonamide	1.4 ± 0.3	--
	N-(3,4-Dimethyl-5-isoxazolyl)benzo-2,1,3-thiadiazole-4-sulfonamide	0.37 ± 0.03	--
35	N-(4-Bromo-3-methyl-5-isoxazolyl)benzo-2,1,3-thiadiazole-4-sulfonamide	0.073 ± 0.048	36 ± 20

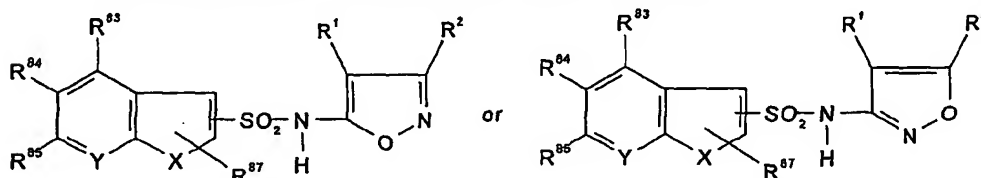
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	COMPOUND	ET _A (μM)*	ET _B (μM)*
	5-chloro-1,3-dimethyl-N-(4-chloro-3-methyl-5-isoxazolyl)pyrazole-4-sulfonamide	0.19 ± 0.03	26 ± 2
	5-chloro-1,3-dimethyl-N-(4-bromo-3-methyl-5-isoxazolyl)pyrazole-4-sulfonamide	0.15 ± 0.03	22 ± 2
5	3,5-dimethyl-N-(4-bromo-3-methyl-5-isoxazolyl)isoxazole-4-sulfonamide	5.35 ± 0.05	78 ± 2

* results based on 1 to 4 experiments

e. Ar² is a fused bicyclic heterocycle with two or more heteroatoms

10 The compounds of this embodiment have formulae IX:



- in which Y is N or O⁺; X is S, O, NR¹¹, in which R¹¹ contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁵ and S(O)_nR¹⁵ in which n is 0-2; R¹⁵ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R¹¹ and R¹⁵ are unsubstituted or are substituted with one or more substituents each selected independently from Z, which is hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁶, CO₂R¹⁶, SH, S(O)_nR¹⁶ in which n is 0-2, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶; R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹², which is selected independently from R¹¹ and Z, is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2; and R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R¹¹, R¹², R¹⁵ and R¹⁶ may be further substituted with the any of the groups set forth for Z;
- R¹ and R² are either (i), (ii) or (iii) as follows:

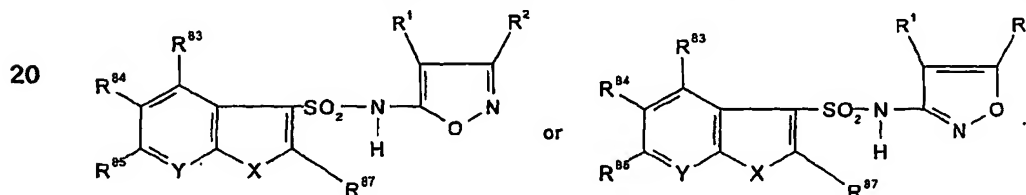
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- (i) R^1 and R^2 are each independently selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, alkyloxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons; or,
- (ii) R^1 and R^2 together form $-(CH_2)_n$, where n is 3 to 6; or,
- (iii) R^1 and R^2 together form 1,3-butadienyl;
- R^{83} , R^{84} and R^{85} are selected from (i), (ii), (iii) or (iv):
- (i) R^{83} , R^{84} and R^{85} are each selected independently from among H, $NHOH$, NH_2 , NO_2 , N_3 , halide, pseudohalide, alkyl, alkenyl, alkynyl, alkylaryl, aryloxy, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxyalkyl, alkylsufinyl, alkylsulfonyl, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl or amido, where the alkyl, alkenyl, alkynyl portions are straight or branched chains of from about 1 up to about 10 carbons, preferably 1 to about 5 or 6 carbons and the aryl portions contain from 3 up to about 10 carbons, preferably 6 carbons; or, alternatively,
- (ii) two of R^{83} , R^{84} and R^{85} together are substituted or unsubstituted 1,3-butadienyl, 4-dimethylamino-1,3 butadienyl, 1-chloro-1,3-butadienyl, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and the others of R^{83} , R^{84} and R^{85} are as defined in (i) above; or alternatively,
- (iii) R^{84} is H; and R^{83} and R^{85} are each independently selected from alkyl, alkoxy, halide, aminoalkyl, dialkylaminoalkyl, in which the alkyl and alkoxy groups contain from 1 to 10, preferably 1 to 6 carbons, and are straight or branched chains; or
- (iv) any two of R^{83} , R^{84} and R^{85} , which are each selected as in (i) form fused carbocyclic or heterocyclic rings; and
- R^{87} is hydrogen or contains up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, and is selected hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{18}$, CO_2R^{18} , $(CH_2)_rR^{18}$, $(CH_2)_rCOR^{18}$, $(CH_2)_rCO(CH_2)_sR^{18}$, SH, $S(O)_n$, $(CH_2)_r$, $S(O)_nR^{18}$ in which n is 0-2, and s and r are each independently 0 to 6, preferably 1-3, $HNOH$, $NR^{18}R^{19}$, NO_2 , N_3 , OR^{18} , $R^{19}NCOR^{18}$ and

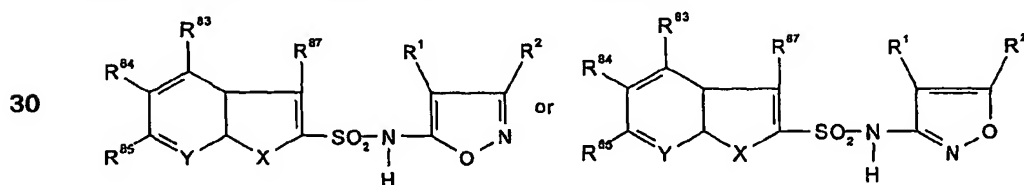
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- CONR¹⁹R¹⁸, in which R¹⁹ is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²⁰, S(O)_nR²⁰ in which n is 0-2; and R¹⁸ and R²⁰ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; and any of the groups set forth for R⁸⁷ is unsubstituted or substituted with any substituents set forth for Z, which is hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R²¹, CO₂R²¹, SH, S(O)_nR²¹ in which n is 0-2, NHOH, NR²²R²¹, NO₂, N₃, OR²¹, R²²NCOR²¹ and CONR²²R²¹; R²² is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²³ and S(O)_nR²³ in which n is 0-2; and R²¹ and R²³ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl.
- R⁸⁷ is preferably C(O)R¹⁸, CO₂R¹⁸, (CH₂)_rR¹⁸, (CH₂)_rCOR¹⁸, (CH₂)_rCO(CH₂)_sR¹⁸, NR¹⁸R¹⁹, OR¹⁸, R¹⁹NCOR¹⁸ or CONR¹⁹R¹⁸.

More preferred compounds are those of formula (IX) that have formula (XXV):



Also of interest of compounds of formula (XXVI):

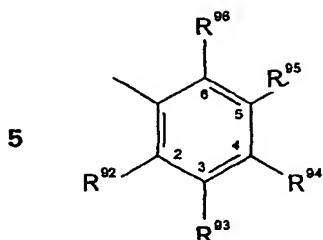


In preferred embodiments of the compounds herein, particularly the compounds of formulae (XXV) and (XXVI), R⁸⁷ is C(O)R¹⁸, CO₂R¹⁸, (CH₂)_rR¹⁸, (CH₂)_rC(O)CH₂)₃R¹⁸, NR¹⁸R¹⁹, OR¹⁸, R¹⁹NCOR¹⁸ and CONR¹⁹R¹⁸ in which r is 0 to 6, preferably 1-3,

When R⁸⁷, R¹⁸ or R¹⁹ is aryl, particularly phenyl, or includes an aryl group, particularly phenyl:

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10

it is unsubstituted or substituted at positions 2-6 with one or more of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} , respectively, which are each independently selected from (i), (ii) or (iii) as follows:

- (i) R^{92} , R^{93} , R^{94} , R^{95} , and R^{96} are each independently selected from among
- 15 H, NHR^{38} , CONR^{38} , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxy, haloalkyl, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, alkylcarbonyl, alkenylthio, alkenylamino, alkenyloxy, alkenylsulfinyl, alkenylsulfonyl, aminocarbonyl, carboxy, carboxyalkyl, carboxyalkenyl, and formyl, where R^{38} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, haloalkyl alkylaryl,
- 20 heterocycle, arylalkyl, arylalkoxy, alkoxy, aryloxy, cycloalkyl, cycloalkenyl and cycloalkynyl, and is preferably hydrogen, lower alkyl, lower alkoxy and lower haloalkyl; or
- (ii) at least two of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} are substituting adjacent carbons on the ring and together form alkylenedioxy, alkylenethioxyoxy or alkylenedithioxy (i.e. $-\text{O}-(\text{CH}_2)_n-\text{O}-$, $-\text{S}-(\text{CH}_2)_n-\text{O}-$, $-\text{S}-(\text{CH}_2)_n-\text{S}-$, where n is 1 to 4,
- 25 preferably 1 or 2), which is unsubstituted or substituted by replacing one or more hydrogens with halide, lower alkyl, lower alkoxy or halo(lower)alkyl, and the others of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} are selected as in (i); or
- (iii) at least two of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} are substituting adjacent carbons on the ring and together form alkylenedioxy, alkylenethioxyoxy or
- 30 alkylenedithioxy (i.e. $-\text{O}-(\text{CH}_2)_n-\text{O}-$, $-\text{S}-(\text{CH}_2)_n-\text{O}-$, $-\text{S}-(\text{CH}_2)_n-\text{S}-$, where n is 1 to 4, preferably 1 or 2), which is unsubstituted or substituted by replacing one or more hydrogens with halide, lower alkyl, lower alkoxy or halo(lower)alkyl, and at least two of the others of R^{93} , R^{94} , R^{95} , and R^{96} are substituting adjacent carbons on the ring and together form alkylenedioxy, alkylenethioxyoxy or alkylenedithioxy (i.e. $-\text{O}-(\text{CH}_2)_n-\text{O}-$,
- 35 $-\text{S}-(\text{CH}_2)_n-\text{O}-$, $-\text{S}-(\text{CH}_2)_n-\text{S}-$, where n is 1 to 4, preferably 1 or 2), which is unsubstituted or substituted by replacing one or more hydrogens with halide, lower alkyl, lower alkoxy or halo(lower)alkyl, and the other of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} is selected as in (i).

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Preferably at least one, more preferably two, of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} is H and the others are selected from among (i), (ii) or (iii) as follows:

- (i) alkoxy, halo, alkylcarbonyl, formyl, and alkyl, in which the alkyl portions or groups contain from 1 to 3 carbons, provided that at least one of R^{92} , R^{93} , R^{94} , R^{95} , and R^{96} is H;
- (ii) at least two of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} are substituting adjacent carbons and together form alkylenedioxy and the others of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} are selected as set forth in (i); or
- (iii) at least two of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} are substituting adjacent carbons and together form alkylenedioxy, and at least two of the others of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} are substituting adjacent carbons and together form alkylenedioxy, and the other of R^{92} , R^{93} , R^{94} , R^{95} and R^{96} is H.

More preferably, at least one of R^{92} and R^{96} is not hydrogen.

- When R^{87} , R^{18} or R^{19} is pyrimidyl, it is substituted with one or more substituents selected from (i) or (ii)

- (i) H, NHR^{38} , $CONR^{38}$, NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxy, haloalkyl, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, alkylcarbonyl, alkenylthio, alkenylamino, alkenyloxy, alkenylsulfinyl, alkenylsulfonyl, aminocarbonyl, carboxy, carboxyalkyl, carboxyalkenyl, and formyl, where R^{38} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, haloalkyl, alkylaryl, heterocycle, arylalkyl, arylalkoxy, alkoxy, aryloxy, cycloalkyl, cycloalkenyl and cycloalkynyl, and is preferably hydrogen, lower alkyl, lower alkoxy and lower haloalkyl; or

- (ii) at least two substituents are on adjacent members of the ring and together form alkylenedioxy, alkylenethioxyoxy or alkylenedithioxy (i.e. $-O-(CH_2)_n-O-$, $-S-(CH_2)_n-O-$, $-S-(CH_2)_n-S-$, where n is 1 to 4, preferably 1 or 2), which is unsubstituted or substituted by replacing one or more hydrogens with halide, lower alkyl, lower alkoxy or halo(lower)alkyl, and the others substituent(s) are selected as in (i).

- In preferred compounds R^{87} is $(CH_2)_4R^{18}$, and R^{18} is phenyl or pyrimidyl, preferably phenyl, in which at least two of substituents are on adjacent members of the ring and form alkylenedioxy, one or two remaining substituents are lower alkyl or lower alkoxy, preferably methyl or methoxy, more preferably methyl, and the others are hydrogen.

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In preferred compounds of all of the embodiments herein, Y is preferably N, and X is preferably S or O, more preferably S.

Among the preferred compounds are those set forth in Table 10:

TABLE 10*

5	COMPOUND	ET _A (μM) [†]	ET _B (μM) [†]
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-ethylthieno[2,3-b]pyridine-3-sulfonamide	.068	39
	N-(4-chloro-5-methyl-3-isoxazolyl)-2-ethylthieno[2,3-b]pyridine-3-sulfonamide	.045	30
10	N-(4-chloro-3-methyl-5-isoxazolyl)thieno[2,3-b]pyridine-3-sulfonamide	1.8	> 100
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)benzoyl]thieno[2,3-b]pyridine-3-sulfonamide	0.96	31
15	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)benzyl]thieno[2,3-b]pyridine-3-sulfonamide	0.0056	2.8
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4,5-methylenedioxy)-2-methylbenzyl]thieno[2,3-b]pyridine-3-sulfonamide	0.0015	31
20	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2,4-dimethyl)benzyl]thieno[2,3-b]pyridine-3-sulfonamide	0.0045	1.5
	N-(4-chloro-5-methyl-3-isoxazolyl)-2-[(4,5-methylenedioxy)-2-methylbenzyl]thieno[2,3-b]pyridine-3-sulfonamide	0.0010	0.5
25	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4,5-methylenedioxy)-2-[(hydroxyethyl)benzyl]]thieno[2,3-b]pyridine-3-sulfonamide	0.0015	3.6
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[1-naphthalene-methyl]thieno[2,3-b]pyridine-3-sulfonamide	0.034	0.56
30	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2,6-dimethoxy)benzyl]thieno[2,3-b]pyridine-3-sulfonamide	0.65	10.1
	N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3-(3,4-methylenedioxyphenyl)propionyl]thieno[2,3-b]pyridine-3-sulfonamide	0.045	6.6
35			

[†] assay performed with incubation at 24° C. As described in the Examples, incubation at this higher temperature reduces the activity by a factor of 2- to about 10-compared to the activity at 4° C

40 * results are generally the average of 2 to 3 experiments

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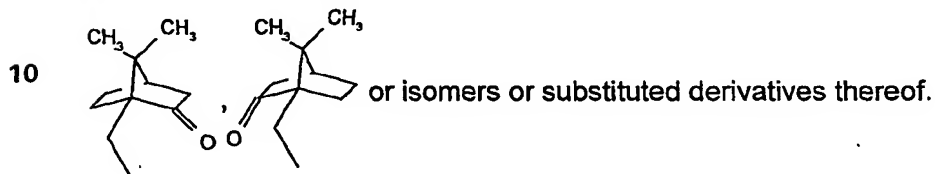
-- data not available or measured as % inhibition @ 100 μ M

% = % inhibition @ 100 μ M

3. Compounds in which Ar² is alkyl

Compounds in which Ar² is alkyl include compounds in which Ar² is CH₃-(CH₂)_n,

5 where n is 0 to about 30, preferably, 0 to 20, and more preferably between about 5 and about 10 and which may be substituted with halide, amino, carbonyl, nitro, and the like, and compounds in which Ar² is



15 R¹ and R² are selected as described above for the thienyl, furyl and pyrrolyl compounds. The methyl groups may be replaced by other lower alkyl groups, hydrogen or halide.

Selected compounds have the following activities:

TABLE 11

20	COMPOUND	ET _A (μ M)	ET _B (μ M)
	N-(3,4-dimethyl-5-isoxazolyl)-(-)-10-camphorsulfonamide	11.9 \pm 0.4	~100
	N-(3,4-Dimethyl-5-isoxazolyl)methanesulfonamide	57*	21*
25	N-(3,4-Dimethyl-5-isoxazolyl)-(+)-10-camphorsulfonamide	20 \pm 2.5	48.2 \pm 3.6
	N-(4-Tridecyl-3-trifluoromethyl-5-isoxazolyl)methanesulfonamide	17.1 \pm 1.0	5.8 \pm 2.0
	N-(3,4-dimethyl-5-isoxazolyl)octyl-1-sulfonamide	3.74	2.88

* preliminary results

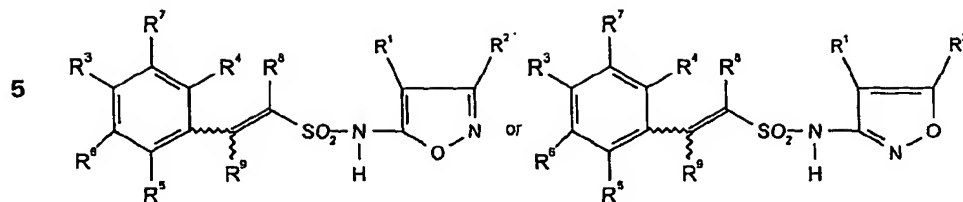
30 4. Compounds in which Ar² is styryl

Compounds in which Ar² is styryl are provided. These compounds have formulae (XXVII):

35

40

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in which R¹ and R² are selected as described above for the thienyl, furyl and pyrrolyl compounds and; R¹-R⁹ are as defined above, R⁸ and R⁹ may be *cis* or *trans* position. Compounds in which Ar² is styryl include, but are not limited to:

15 N-(3,4-dimethyl-5-isoxazolyl)- β -*trans*-styrenesulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)- β -*trans*-styrenesulfonamide, N-(4-bromo-5-methyl-3-isoxazolyl)- β -*trans*-styrenesulfonamide, 2-nitro-N-(3,4-dimethyl-5-isoxazolyl)styrenesulfonamide, 2-nitro-N-(4-bromo-3-methyl-5-isoxazolyl)styrenesulfonamide, 2-nitro-N-(4-bromo-5-methyl-3-isoxazolyl)styrenesulfonamide, 1,2-*trans*-dimethyl-N-(3,4-dimethyl-5-isoxazolyl)styrene-

20 1-sulfonamide, 1,2-*trans*-dimethyl-N-(4-bromo-3-methyl-5-isoxazolyl)styrene-1-sulfonamide, 1,2-*trans*-dimethyl-N-(4-bromo-5-methyl-3-isoxazolyl)styrene-1-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-2-phenylstyrene-1-sulfonamide, N-(4-bromo-5-methyl-3-isoxazolyl)-2-phenylstyrene-1-sulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-2-phenylstyrene-1-sulfonamide, 1,2-*cis*-dimethyl-N-(3,4-dimethyl-5-isoxazolyl)styrene-1-sulfonamide, 1,2-*cis*-dimethyl-N-(4-bromo-3-methyl-5-isoxazolyl)styrene-1-sulfonamide and 1,2-*cis*-dimethyl-N-(4-bromo-5-methyl-3-isoxazolyl)styrene-1-sulfonamide. The activities of exemplary compounds are set forth in Table 12.

25

TABLE 12

30	COMPOUND	ET _A (μ M)*	ET _B (μ M)*
	N-(3,4-dimethyl-5-isoxazolyl)- β - <i>trans</i> -styrene-sulfonamide	12	21
	2-nitro-N-(3,4-dimethyl-5-isoxazolyl)- β - <i>trans</i> -styrene-sulfonamide	15	61.5
35	1,2- <i>cis</i> -dimethyl-N-(3,4-dimethyl-5-isoxazolyl)styrene-1-sulfonamide	35	37
	1,2- <i>trans</i> -dimethyl-N-(3,4-dimethyl-5-isoxazolyl)styrene-1-sulfonamide	9	--

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COMPOUND	ET _A (μM)*	ET _B (μM)*
N-(3,4-dimethyl-5-isoxazolyl)-2-phenylstyrene-1-sulfonamide	4	~50

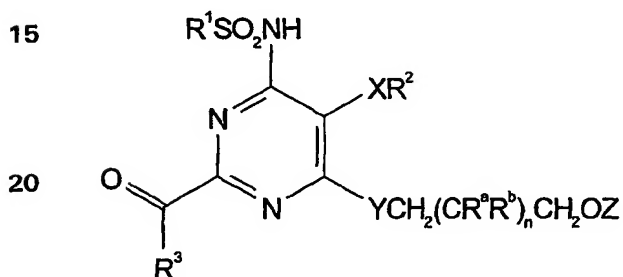
* preliminary results

5 5. **Other endothelin receptor antagonists**

Any endothelin receptor antagonist, or any compound that alters or otherwise modulates endothelin activity, is intended for use in the methods provided herein. In particular, endothelin receptor antagonists disclosed in the following documents are contemplated for use in the methods provided herein.

10 a. **U.S. Patent No. 5,856,484**

In particular, compounds of formula I are intended for use in the methods provided herein:



25 wherein R¹ is phenyl, substituted phenyl or heterocyclyl; R² is phenyl or substituted phenyl; R³ is hydroxy, lower-alkoxy or a residue -NR⁴R⁵; R⁴ is hydrogen or a residue -R⁶ and R⁵ is hydrogen or a residue -(CH₂)_mR⁶ or R⁴ and R⁵ together with the N atom to which they are attached are in N heterocyclic residue; R⁶ is phenyl, substituted phenyl, 30 cycloalkyl, heterocyclyl, lower-alkyl, hydroxy-lower-alkyl, amino-lower-alkyl, carboxy-lower-alkyl or lower-alkoxycarbonyl-lower-alkyl; R^a is hydrogen, lower-alkyl or hydroxy; R^b is hydrogen or lower-alkyl; X is oxygen or sulphur; Y is oxygen or sulphur; Z is hydrogen, lower-alkyl, aryl, aryl-lower-alkyl, hetero-cyclyl or heterocyclyl-lower-alkyl; m is 0, 1 or 2; and n is 0, 1 or 2; and pharmaceutically acceptable salts thereof.

35 Preferred compounds of this embodiment are those where R¹ is phenyl; a substituted phenyl substituted by a chemical group selected from the group consisting of lower alkyl, lower alkoxy, methylenedioxy, ethylenedioxy, lower-alkanoyl, hydroxy, amino, mono-lower-alkylamino, di-lower-alkylamino or halogen; or heterocyclyl selected

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- from the group consisting of 2-furyl, 3-furyl, pyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-tetrazolyl-4-pyridyl, 1,2-diazinyl, 1,4-diazinyl, morpholino, 2-thienyl, 3-thienyl, isoxazolyl, oxazolyl, thiazolyl, imidazolyl, pyrrolyl and tetrazolyl; R² is phenyl or a substituted phenyl substituted by a chemical group selected from the group consisting
- 5 of lower alkyl, lower alkoxy, methylenedioxy, ethylenedioxy, lower-alkanoyl, hydroxy, amino, mono-lower-alkylamino, di-lower-alkylamino and halogen; R³ is hydroxy, lower alkoxy or -R⁴ R⁵; R⁴ is hydrogen or -R⁶ and R⁵ is hydrogen or -(CH₂)_mR⁶ or R⁴ and R⁵ together are an N-heterocyclic chosen from the group consisting of morpholino, piperidino, piperazino and N⁴-lower-alkylpiperazino; R⁶ is phenyl; cycloalkyl; lower-alkyl;
- 10 hydroxy lower alkyl; amino-lower-alkyl; carboxy-lower-alkyl; lower-alkoxycarbonyl-lower-alkyl; a substituted phenyl substituted by a chemical group selected from the group consisting of lower alkyl, lower alkoxy, methylenedioxy, ethylenedioxy, lower-alkanoyl, hydroxy, amino, mono-lower-alkylamino, di-lower-alkylamino or halogen; or heterocyclyl chosen from the group consisting of 2-furyl, 3-furyl, pyrimidinyl,
- 15 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-tetrazolyl-4-pyridyl, 1,2-diazinyl, 1,4-diazinyl, morpholino, 2-thienyl, 3-thienyl, isoxazolyl, oxazolyl, thiazolyl, imidazolyl, pyrrolyl and tetrazolyl; R^a is hydrogen, lower-alkyl or hydroxy; R^b is hydrogen or lower alkyl; X is oxygen or sulfur; Y is oxygen or sulfur; Z is hydrogen; lower-alkyl; aryl; aryl-lower-alkyl; heterocyclyl selected from the group consisting of 2-furyl, 3-furyl, pyrimidinyl, 2-pyridyl,
- 20 3-pyridyl, 4-pyridyl, 2-tetrazolyl-4-pyridyl, 1,2-diazinyl, 1,4-diazinyl, morpholino, 2-thienyl, 3-thienyl, isoxazolyl, oxazolyl, thiazolyl, imidazolyl, pyrrolyl and tetrazolyl; or heterocyclyl selected from the group consisting of 2-furyl, 3-furyl, pyrimidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-tetrazolyl-4-pyridyl, 1,2-diazinyl, 1,4-diazinyl, morpholino, 2-thienyl, 3-thienyl, isoxazolyl, oxazolyl, thiazolyl, imidazolyl, pyrrolyl and tetrazolyl,
- 25 wherein the heterocyclyl is substituted with lower-alkyl; m is 0, 1, or 2; and, n is 0, 1, or 2; and pharmaceutically acceptable salts thereof.

- Particularly preferred compounds of this embodiment include 6-(4-tert-butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid phenylamide; (RS)-4-(4-tert-Butyl-phenylsulphonylamino)-6-(2,3-
- 30 dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (3-hydroxy-phenyl)-amide; 4-(4-tert-Butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (3-hydroxy-phenyl)-amide; 4-(4-tert-Butyl-phenylsulphonylamino)-6-(2-hydroxyethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (3-hydroxymethyl-phenyl)-amide; 4-(4-tert-Butyl-phenylsulphonylamino)-

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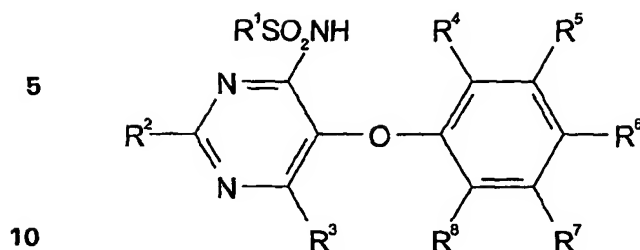
6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (2-hydroxy-methylphenyl)amide; 6-(4-tert-Butyl-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-4-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide; 4-(4-tert-Butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid phenylamide; 6-(4-tert-butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid; (RS)-6-(4-tert-butyl-phenylsulphonylamino)-4-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid; 6-(4-tert-butyl-phenylsulphonylamino)-4-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidine-2-carboxylic acid; 4-(4-tert-butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidine-2-carboxylic acid; 4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid pyridin-3-ylamide; (RS)-4-(4-tert-Butyl-phenylsulphonylamino)-6-(2,3-dihydroxy-propoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid pyridin-3-ylamide; 4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)amide; 6-(4-tert-butylphenylsulphonylamino)-4-(2,3-dihydroxypropoxy)-5-(3-methoxyphenoxy)-pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)amide; 4-tert-Butyl-N-[6-(2-hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-2-(morpholin-4-ylcarboxyl)-pyrimidin-4-yl]-benzenesulphonamide; 4-(2-Hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidine-2-carboxylic acid phenylamide; 4-(2-Hydroxy-ethoxy)-5-(3-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonylamino)-pyrimidin-2-carboxylic acid; 4-(2-Hydroxyethoxy)-5-(3-methoxyphenoxy)-6-(5-methyl-pyridin-2-ylsulphonylamino)-pyrimidine-2-carboxylic acid (1 H-tetrazol-5-yl)amide; 4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid; (R,S)-6-(2,3-Dihydroxy-propoxy)-5-(3-methoxyphenoxy)-4-(5-methylpyridin-2-ylsulphonylamino)-pyrimidine-2-carboxylic acid; 4-(2-hydroxy-ethoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(3-methoxy-phenoxy)-pyrimidine-2-carboxylic acid; and 4-(4-tert-butyl-phenylsulphonylamino)-5-(3-methoxy-phenoxy)-6-(2-pyrimidin-2-yloxy-ethoxy)-pyrimidine-2-carboxylic acid.

30 b. U.S. Patent No. 5,837,708

Other compounds for use in the methods provided herein include sulfonamides of the formula:

35

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wherein R¹ is heterocyclyl; R² is selected from the group consisting of hydrogen,
 15 lower-alkyl, lower-alkoxy, lower-alkylthio, lower-alkoxy-lower-alkyl,
 lower-alkylsulphonyl-lower-alkoxy, phenyl, lower alkylphenyl,
 lower-alkoxy-phenyl, lower-alkylenedioxyphenyl, phenyl-lower alkyl, lower
 alkyl-phenyl-lower alkyl, lower alkoxy-phenyl-lower alkyl, lower
 alkylenedioxyphenyl-lower alkyl, heterocyclyl and heterocyclyl-lower alkyl; R³ is selected
 20 from the group consisting of lower-alkyl, lower-alkoxy, formyl, halo-lower-alkyl,
 hydroxy-lower-alkyl, amino-lower-alkyl, -CH₂O-A-lower-alkyl, -(CH₂)ₘ-O-(CRᵃRᵇ)
 ₙOH, -(CH₂)ₘ-O-(CRᵃRᵇ)-ₙORᵃ, -(CH₂)ₘ-O-(CRᵃRᵇ)ₙNH₂ and -(CH₂)ₘ
 -O-(CRᵃRᵇ)ₙ-Y-Rᵃ; R⁴-R⁸ each are selected from the group consisting of hydrogen,
 lower-alkoxy and halogen; R⁹ is selected from the group consisting of heterocyclyl;
 25 phenyl; and phenyl substituted with a group selected from the group consisting of
 lower-alkyl, lower-alkoxy and halogen; Rᵃ and Rᵇ each are hydrogen or lower-alkyl; A is
 a ketalized 1,2-dihydroxy-ethylene group; Y is selected from the group consisting of
 -OC(O)O-, -NH(C(O)NH- and -NHC(O)O-; n is 2, 3 or 4; and m is 0 or 1.

Particularly preferred compounds of this embodiment include

30 5-tert-butyl-thiophene-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-
 2,2'-bipyrimidin-4-ylamide, 5-pentyl-thiophene-2-sulphonic acid 6-(2-hydroxy-ethoxy)-
 5-(2-methoxy-phenoxy)-2,2'-bipyrimidin-4-ylamide, 5-(2,2-dimethyl-propionyl)-thiophene-
 2-sulphonic acid, 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2,2'-bipyrimidin-4-
 ylamide, 5-isopropyl-pyridine-2-sulphonic acid 6-(2-hydroxy-thoxy)-5-2-methoxy-
 35 phenoxy)-2,2'-bipyrimidin-4-ylamide, pyridine-3-sulphonic acid 6-(2-hydroxy-ethoxy)-
 5-(2-methoxy-phenoxy)-2,2'-bipyrimidin-4-ylamide, 5-tert-butyl-thiophene-2-sulphonic
 acid 5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-ylamide,
 5-tert-butyl-thiophene-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-
 pyrimidin-4-ylamide, N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-

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- 4-yl-5-isopropyl-pyridine-2-sulphonamide, 5-isopropyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(3-methoxy-phenyl)-pyrimidin-4-yl-pyridine-2-sulphonamide, 5-isopropyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-methylsulphanyl-pyrimidin-4-yl-pyridine-2-sulphonamide, N-[2-(1, 3-benzodioxol-5-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl-5-isopropyl-pyridine-2-sulphonamide, N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-morpholin-4-yl-pyrimidin-4-yl-5-isopropyl-pyridine-2-sulphonamide, 5-methyl-pyridine-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2,2'-bipyrimidin-4-ylamide, 5-methyl-pyridine-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-ylamide, 5-isopropyl-pyridine-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-ylamide, 5-tert-butylthiophene-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-yl amide, 2,5-dichlorothiophene-3-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-ylamide, 3,5-dimethylisoxazole-4-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-ylamide, 2,5-dichlorothiophene-3-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2,2'-bipyrimidin-4-ylamide, and 3,5-dimethyl-isoxazole-4-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2,2'-bipyrimidin-4-ylamide; pyridin-2-ylcarbamic acid 2-[6-(5-tert-butyl-thiophen-2-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2,2'-bipyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[5-(2-methoxy-phenoxy)-6-(5-pentyl-thiophen-2-ylsulphonylamino)-2,2'-bipyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[6-[5-(2,2-dimethylpropionyl)-thiophen-2-ylsulphonylamino]-5-(2-methoxy-phenoxy)-2,2'-bipyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2,2'-bipyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[5-(2-methoxy-phenoxy)-6-pyridin-2-ylsulphonylamino)-2,2'-bipyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[5-(2-methoxy-phenoxy)-6-pyridin-3-ylsulphonylamino)-2,2'-bipyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[6-(5-tert-butyl-thiophen-2-ylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl ester, pyridin-4-ylcarbamic acid 2-[6-(5-tert-butyl-thiophen-2-ylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2-(3-methoxy-phenyl)-pyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2-methylsulphanyl-pyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[2-(1,3-

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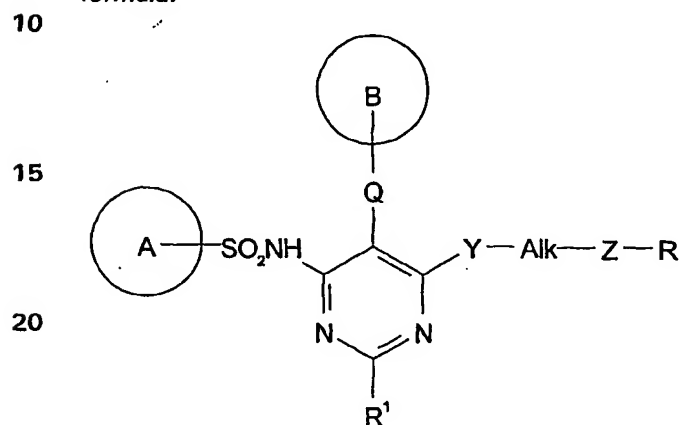
- benzodioxol-5-yl)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(2-methoxy-phenoxy)-pyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[5-(2-chloro-5-methoxy-phenoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-2-morpholin-4-ylpyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[5-(2-methoxy-phenoxy)-6-(5-methyl-pyridin-2-ylsulphonylamino)-2,2'-bipyridimin-4-yloxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[5-(2-methoxy-phenoxy)-6-(5-methyl-pyridin-2-ylsulphonylamino)-2-morpholin-4-yl-pyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[5-(2-chloro-5-methoxy-phenoxy)-6-(5-isopropyl-pyridin-2-sulphonylamino)-2-morpholin-4-yl-pyrimidin-4-yl-methoxy]-ethyl ester, pyridin-2-ylcarbamic acid 5-(2-chloro-5-methoxy-phenoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-2-morpholin-4-yl-pyrimidin-4-ylmethyl ester, pyridin-2-ylcarbamic acid 2-[6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2-morpholin-4-ylpyrimidin-4-yloxy]ethyl ester, pyridin-2-ylcarbamic acid 2-[6-(2,5-dichlorothiophen-3-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2,2'-bipyrimidin-4-yloxy]ethyl ester, pyridin-2-ylcarbamic acid 2-[5-(2-methoxy-phenoxy)-6-(3,5-dimethyl-isoxazol-4-ylsulphonylamino)-2,2'-bipyrimidin-4-yloxy]ethyl ester, pyridin-2-ylcarbamic acid 2-[6-(5-tert-Butylthiophen-2-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[6-(2,5-dichloro-thiophen-3-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-yloxy]-ethyl ester, pyridin-2-ylcarbamic acid 2-[6-(3,5-dimethyl-isoxazol-4-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-yloxy]-ethyl ester, carboxylic acid furan-3-ylmethyl ester 2-[5-(2-methoxy-phenoxy)-6-(5-methyl-pyridin-2-sulphonylamino)-2-morpholin-4-yl-pyrimidin-4-yloxy]-ethyl ester, 5-tert-butyl-thiophene-2-sulphonic acid, 5-(2-methoxy-phenoxy)-6-[2-(3-pyridin-2-yl-ureido)-ethoxy]-2,2'-bipyrimidin-4-ylamide, 5-isopropyl-pyridine-2-sulphonic acid 5-(2-methoxy-phenoxy)-6-[2-(3-pyridin-2-yl-ureido)-ethoxy]-2,2'-bipyrimidin-4-ylamide, 5-isopropyl-pyridine-sulphonic acid [6-(2-hydroxy-ethoxy)-2-(3-methoxy-benzyl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide, 5-isopropyl-pyridine-2-sulphonic acid [6-(2-hydroxy-ethoxy)-2-(3-methoxy-benzyl)-5-phenoxy-pyrimidin-4-yl]-amide, 5-isopropyl-pyridine-2-sulphonic acid [2-(3-hydroxy-benzyl)-6-(2-hydroxy-ethoxy)-5-phenoxy-pyrimidin-4-yl]-amide, 5-isopropyl-pyridine-2-sulphonic acid [6-(2-hydroxy-ethoxy)-2-(3-methoxy-benzyl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide, 5-isopropyl-pyridine-2-sulphonic acid [6-(2-hydroxy-ethoxy)-2-(3-methoxy-benzyl)-5-phenoxy-pyrimidin-4-yl]-amide, 5-isopropyl-pyridine-2-sulphonic acid [2-(3-hydroxy-benzyl)-6-(2-hydroxy-ethoxy)-5-phenoxy-pyrimidin-4-yl]-amide, 5-isopropyl-pyridine-2-sulphonic acid 5-(2-chloro-5-methoxy-phenoxy)-6-methyl-2-morpholin-4-yl-

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pyrimidin-4-ylamide, 5-(2-chloro-5-methoxy-phenoxy)-6-formyl-2-morpholin-4-yl-pyrimidin-4-ylamide, 5-isopropyl-pyridine-2-sulphonic acid 5-(2-chloro-5-methoxy-phenoxy)-6-hydroxymethyl-2-morpholin-4-yl-pyrimidin-4-ylamide, 5-isopropyl-pyridine-2-sulphonic acid, 5-(2-chloro-5-methoxy-phenoxy)-6-chloromethyl-2-morpholin-4-yl-pyrimidin-4-ylamide, and 5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxymethyl)-2-morpholin-4-yl-pyrimidin-4-ylamide.

c. U.S. Patent No. 5,739,333

Also intended for use in the methods provided herein are sulfonamides of formula:



wherein Ring A and Ring B are a substituted or unsubstituted monocyclic, bicyclic or tricyclic hydrocarbon group, or a substituted or unsubstituted heterocyclic group, Q is a single bond or a group of the formula: $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-CH_2-$, Y is a group of the formula: $-O-$, $-S-$ or $-NH-$, Alk is a lower alkylene group or a lower alkenylene group, Z is a group of the formula: $-O-$ or $-NH-$, R is a substituted or unsubstituted aromatic heterocyclic or aryl group, R¹ is a hydrogen atom, a substituted or unsubstituted amino group, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a substituted or unsubstituted lower alkynyl group, a substituted or unsubstituted lower alkylthio group, a substituted or unsubstituted lower alkoxy group, or a substituted or unsubstituted heterocyclic group or a substituted or unsubstituted aryl group, or a pharmaceutically acceptable salt thereof.

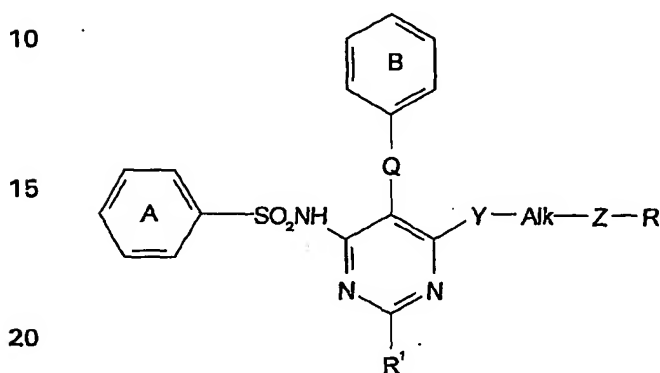
Particularly preferred compounds of this embodiment include N-[6-[2-[(5-Bromopyrimidin-2-yl)oxy]ethoxy]-2-(4-hydroxypiperidino)-5-(2-methoxyphenoxy)pyrimidin-4-yl]-4-tert-butylbenzenesulfonamide, N-[2-[(2-

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Methoxyethyl)amino]-5-(2-methoxyphenoxy)-6-[2-[(5-methoxypyrimidin-2-yl)oxy]ethoxy[pyrimidin-4-yl]-4-tert-butylbenzenesulfonamide, N-[6-[2-[(5-Bromopyrimidin-2-yl)oxy]ethoxy]-2-[(2-hydroxyethyl)amino]-5-(4-methylphenyl)pyrimidin-4-yl]-4-tert-butylbenzenesulfonamide, or pharmaceutically acceptable salts thereof.

d. U.S. Patent No. 5,728,706

Other compounds for use in the methods provide herein include sulfonamides of formula:

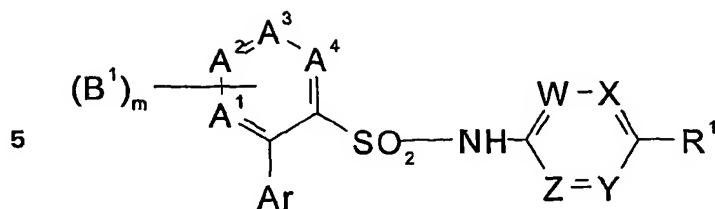


wherein Ring A and Ring B are the same or different and each is a substituted or unsubstituted benzene ring, Q is a single bond or a group of the formula: $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-CH_2-$, Y is a group of the formula: $-O-$, $-S-$ or $-NH-$, Alk is a lower alkylene group or a lower alkenylene group, Z is a single bond or a group of the formula: $-O-$ or $-NH-$, R is a substituted or unsubstituted aromatic heterocyclic or aryl group, R¹ is hydrogen atom, trifluoromethyl group, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a mono- or di-lower alkylamino group, a substituted or unsubstituted lower alkylthio group, a substituted or unsubstituted lower alkoxy group, a substituted or unsubstituted lower alkynyl group, an aromatic heterocyclic group, a substituted or unsubstituted aliphatic heterocyclic group or an aryl group, provided that when Z is a single bond, R is a substituted or unsubstituted aromatic heterocyclic group, or a pharmaceutically acceptable salt thereof.

e. International Patent Application Publication No. WO 96/40681

Other compounds for use in the methods provided herein include sulfonamides of formula:

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- 10 wherein one of A¹, A², A³, and A⁴ is nitrogen and the remainder of A¹, A², A³, and A⁴ are CH; Ar is a phenyl group which is unsubstituted or bears 1, 2 or 3 substituents independently selected from (1-6C)alkyl, amino(1-6C)alkyl, hydroxy(1-6C)alkyl, N-[(1-4C)alkyl]amino(1-6C)alkyl, N,N-[di(1-4C)alkyl]amino(1-6C)alkyl, carboxy(1-6C)alkyl, (1-6C)alkoxycarbonyl(1-6C)alkyl, (1-6C)alkylcarbonyloxy(1-6C)alkyl, carbamoyl(1-6C)alkyl,
- 15 N-(1-6C)alkylcarbamoyl(1-6C)alkyl, di-N-(1-6C)alkylcarbamoyl(1-6C)alkyl, N-(1-6C)alkylcarbamoyloxy(1-6C)alkyl, carboxy(1-6C)alkoxy, carboxy(1-6C)alkylthio, (1-6C)alkoxycarbonyl(1-6C)alkoxy, (1-6C)alkoxycarbonyl(1-6C)alkylthio, carbamoyl(1-6C)alkoxy, (1-6C)alkylcarbamoyl(1-6C)alkoxy, di(1-6C)alkylcarbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkylthio, (1-6C)alkylcarbamoyl(1-6C)alkylthio, di(1-6C)alkylcarbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkylthio, (1-6C)alkylcarbamoyl(1-6C)alkylthio, di(1-6C)alkylcarbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkylthio, (1-6C)alkylcarbamoyl(1-6C)alkylthio, (1-6C)alkylcarbamoyl(1-6C)alkylthio, (2-6C)alkenyl, carboxy(2-6C)alkenyl, (2-6C)alkynyl, carboxy(2-6C)alkynyl, halogen(2-6C)alkyl, trifluoromethyl, trichloromethyl, tribromomethyl, (1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihalogeno(1-6C)alkoxy, trihalogeno(1-6C)alkoxy, (2-6C)alkenyloxy(1-6C)alkyl, (2-6C)alkenyloxy, (1-4C)alkoxy(1-6C)alkyl, (1-6C)alkoxycarbonyl(1-6C)alkoxy(1-6C)alkyl, carboxy(1-6C)alkoxy(1-6C)alkyl, hydroxy(1-6C)alkoxy(1-6C)alkyl, (1-4C)alkylthio(1-6C)alkyl, (1-4C)alkylsulphanyl(1-6C)alkyl, (1-4C)alkylsulphonyl(1-6C)alkyl, (1-4C)alkylenedioxy, (3-6C)cycloalkyl, (3-8C)cycloalkyl(1-6C)alkyl, phenyl, phenyl(1-6C)alkyl, phenoxy, phenyl(1-6C)alkoxy, pyridyl(1-6C)alkoxy(1-6C)alkyl, halogeno, hydroxy, mercapto, cyano, nitro, carboxy, (1-6C)alkoxycarbonyl, (2-6C)alkenyloxycarbonyl, phenyloxycarbonyl, phenyl(1-6C)alkoxycarbonyl, (1-6C)alkanoyl, benzoyl, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, phenylthio, phenylsulphanyl, phenylsulphonyl, (1-6C)alkanoylamino, trifluoroacetyl, trifluoroacetamido, N,[(1-4C)alkyl]trifluoroacetamido, benzamido, N,[(1-4C)alkyl]benzamido, carbamoyl, (1-4C)alkylcarbamoyl, di-(1-4C)alkylcarbamoylphenylcarbamoyl, sulphamoyl, N-(1-4C)alkylsulphamoyl, N,N-di-(1-4C)alkylsulphamoyl, N-phenylsulphamoyl, (1-6C)alkanesulphonamido,
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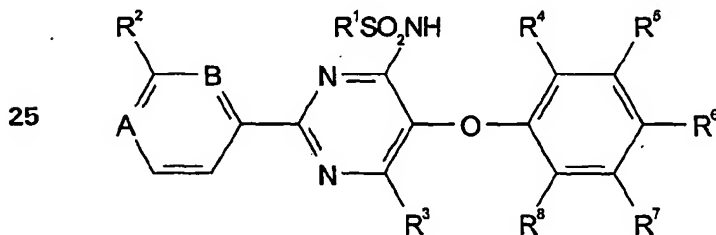
- benezenesulphonamido, ureido, 3-(1-6C)alkylureido, 3-phenylureido, thioureido, 3-(1-6C)alkylthioureido, 3-phenylthioureido, a five membered heterocyclyl group containing 1,2, 3 or 4 heteroatoms independently selected from nitrogen, oxygen and sulphur, a six membered heterocyclyl group containing 1, 2 or 3 heteroatoms independently
- 5 selected from nitrogen, oxygen and sulphur, and a group-NRaRb in which Ra and Rb are independently selected from hydrogen, (1-6C)alkyl, phenyl(1-4C)alkyl and (1-6C)alkyl bearing a carboxy, (1-6C)alkoxycarbonyl, carbamoyl, (1-6C)alkylcarbamoyl or di(1-6C)alkylcarbamoyl group, or the group -NRaRb taken together complete a 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 1-piperidinyl, 2-oxo-1-piperidinyl, morpholino or thiamorpholino ring;
- 10 B¹, is an optional substituent on a carbon atom of A¹, A², A³ or A⁴ selected from (1-4C)alkyl, halogeno and (1-4C)alkoxy; m is zero, 1, 2 or 3; the ring containing W, X, Y and Z and bearing substituent R¹ is selected from: (a) a ring in which W is nitrogen; X is CH; Y is nitrogen; and Z is CR_Y in which R_Y is hydrogen, halogeno, (1-4C)alkyl, (1-4C)alkoxy or trifluoromethoxy; and substituent R¹ is hydrogen, halogeno, (1-4C)alkyl,
- 15 methoxy, ethoxy, trifluoromethyl or ethynyl; (b) a ring in which W is CR_Z in which R_Z is hydrogen, halogeno, (1-4C)alkyl, (1-4C)alkoxy or trifluoromethoxy; X is nitrogen; Y is nitrogen; and Z is CH; and substituent R¹ is halogeno, (1-4C)alkyl, methoxy, ethoxy, trifluoromethyl or ethynyl; and (c) a ring in which W and X are both nitrogen; Y is CH; and Z is CR_X in which R_X is hydrogen, halogeno, (1-4C)alkyl, (1-4C)alkoxy or
- 20 trifluoromethoxy; and substituent R¹ is halogeno, (1-4C)alkyl, methoxy, ethoxy, trifluoromethyl or ethynyl; and wherein any of said phenyl or benzene or heterocyclyl moieties of a substituent on Ar may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl (1-4C)alkoxy, halogeno, cyano, carboxy and trifluoromethyl; or an N-oxide thereof; or a pharmaceutically-acceptable salt thereof.
- 25 Preferred compounds of this embodiment include 2-(4-isobutylphenyl)-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; N-(5-chloro-3-methoxypyrazin-2-yl)-2-(4-isobutylphenyl)pyridine-3-sulphonamide; 2-[4-(1-carboxyethoxy)phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-(4-ethylphenyl)-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-(4-tert-butylphenyl)-N-(3-methoxy-5-
- 30 methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-[4-(3-hydroxy-2-methylpropyl)phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-(4-acetylphenyl)-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-[4-(1-hydroxyethyl)phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-(4-allylphenyl)-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-[4-2-hydroxy-2-

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methylpropyl)phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[3-pyridyl]pyridine-3-sulphonamide; N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[2-pyridyl]phenyl)pyridine-3-sulphonamide; N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide; N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,2,4-oxadiazol-3-yl]phenyl)pyridine-3-sulphonamide; N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[pyrimidin-2-yl]phenyl)pyridine-3-sulphonamide; 2-[4-[(2-hydroxyethoxy)methyl]phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-[4-(2-hydroxyethoxy)phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-[4-(3-acetoxy-2-methylpropyl)phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-[4-(2-carboxypropyl)phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-[4-(2-methylpropanoyl)phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-[4-(2-carboxy-2-methylpropyl)phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; 2-[4-cyclopropylmethylphenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; and 2-[4-(2-propoxycarbonyl-2-methylpropyl)phenyl]-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide; or a pharmaceutically acceptable salt thereof.

f. International Patent Application Publication No. WO 96/19459

In particular, compounds for use in the methods provided herein have the formula:



wherein R^1 signifies aryl or heterocyclyl; R^2 signifies tetrazolyl, lower-alkyl-substituted tetrazolyl, cyano, carboxy, lower-alkoxycarbonyl, hydroxymethyl, formyl, carbamoyl, thiocarbamoyl, amidino or hydroxyamidino; R^3 signifies a residue $-O-(CR^aR^b)_n-OR^9$; R^4 - R^8 signify hydrogen, lower-alkoxy or halogen; R^9 signifies hydrogen, aryl, lower-alkyl, heterocyclyl or a residue $-C(O)NHR^{10}$; R^{10} signifies lower-alkyl, phenyl, substituted phenyl, pyridyl or substituted pyridyl; R^a and R^b signify hydrogen or lower-alkyl; n signifies 2, 3 or 4; and A and B signify CH; or one of the symbols A or B signifies nitrogen and the other signifies CH; or R^2 signifies hydrogen and one of the symbols A

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or B signifies N-oxide (N→O) and the other signifies CH, and pharmaceutically usable salts of compounds of formula I.

- Preferred compounds of this embodiment include 5-methyl-pyridine-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-ylamide, 5-isopropyl-pyridine-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-ylamide, 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide, 2-[6-(4-tert-butyl-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl-oxy]-ethyl pyridin-2-ylcarbamate, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-4-methyl-benzenesulphonamide, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-4-methoxy-benzenesulphonamide, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-4-methylsulphanyl-benzenesulphonamide, 1,3-benzodioxol-5-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-ylamide, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-3,4-dimethoxy-benzenesulphonamide, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-2,5-dimethoxy-benzolsulphonamide, pyridine-3-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-ylamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide, 1,3-benzodioxol-5-sulphonic acid [5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-amide, 5-isopropyl-pyridine-2-sulphonic acid [5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-amide, 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[6-(1H-tetrazol-5-yl)-pyridin-2-yl]-pyrimidin-4-yl]-benzenesulphonamide, 2-[5-(2-methoxy-phenoxy)-6-phenylsulphonylamino-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl-oxy]-ethyl pyridin-2-ylcarbamate, 2-[5-(2-methoxy-phenoxy)-6-(4-methyl-phenylsulphonyl-amino)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl-oxy]-ethyl pyridin-2-ylcarbamate, 2-[5-(2-methoxy-phenoxy)-6-(4-methyl-phenylsulphonyl-amino)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl-oxy]-ethyl 1,3-benzodioxol-5-ylcarbamate, 2-[5-(2-methoxy-phenoxy)-6-(4-

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- methoxy-phenylsulphonyl-amino-2-(2-1H-tetrazol-5-yl-pyridin-2-yl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[5-(2-methoxy-phenoxy)-6-(4-methoxy-phenylsulphonyl-amino-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy)-ethyl 1,3-benzodioxol-5-ylcarbamate, 2-[5-(2-methoxy-phenoxy)-6-(4-methylsulphanylphenyl-sulphonylamino)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[6-(1,3-benzodioxol-5-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[6-(1,3-benzodioxol-5-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy]-ethyl 1,3-benzodioxol-5-ylcarbamate, 2-[6-(3,4-dimethoxy-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[5-(2-methoxy-phenoxy)-6-(2,5-dimethoxy-phenyl-sulphonylamino)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-2-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-6-pyridin-3-ylsulphonylamino-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[5-(2-methoxy-phenoxy)-6-pyridin-3-ylsulphonylamino-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy]-ethyl 1,3-benzodioxol-5-ylcarbamate, 2-[5-(2-methoxy-phenoxy)-6-(5-methyl-pyridin-2-yl-sulphonylamino)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[6-(5-isopropyl-pyridin-2-ylsulphonylamino)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy]-ethyl 1,3-benzodioxol-5-ylcarbamate, 2-[6-(4-tert-butyl-phenylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[6-(1,3-benzodioxol-5-ylsulphonylamino)-5-(2-chloro-5-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[5-(2-chloro-5-methoxy-phenoxy)-6-(5-isopropyl-pyridin-2-ylsulphonylamino)-2-(2-1H-tetrazol-5-yl-pyridin-2-yl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, 2-[6-(4-tert-butyl-phenylsulphonylamino)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-2-yl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, N-[6-(2-benzyloxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide, 5-methyl-pyridine-2-sulphonic acid [6-(2-benzyloxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-amide, 5-isopropyl-pyridine-2-sulphonic acid [6-(2-benzyloxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide, 4-tert-butyl-N-[5-(2-methoxy-phenoxy)-6-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-2-(2-1H-tetrazol-5-yl-

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- pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide, 4-tert-butyl-N-[2-[2-(1-ethyl-1H-tetrazol-5-yl)-pyridin-4-yl]-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]benzenesulphonamide, 4-tert-butyl-N-[2-(3-cyano-phenyl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide, 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(3-1H-tetrazol-5-yl-phenyl)-pyrimidin-4-yl]-benzenesulphonamide, 2-[6-(4-tert-butyl-phenylsulphonyl)-5-(2-methoxy-phenoxy)-2-(3-1H-tetrazol-5-yl-phenyl)-pyrimidin-4-yloxy]-ethyl pyridin-2-ylcarbamate, N-[6-(2-benzyloxy-ethoxy)-2-(3-cyano-phenyl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide, N-[6-(2-benzyloxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(3-1H-tetrazol-5-yl-phenyl)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide, 4-tert-butyl-N-[2-(4-cyano-phenyl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamid, 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(4-1H-tetrazol-5-yl-phenyl)-pyrimidin-4-yl]-benzenesulphonamide, N-[6-(2-benzyloxy-ethoxy)-2-(4-cyano-phenyl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzene-sulphonamide, N-[6-(2-benzyloxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(4-1H-tetrazol-5-yl-phenyl)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide, 4-tert-butyl-N-[2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide, N-[2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide, N-[2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-4-methyl-benzene-sulphonamide, N-[2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-4-methoxy-benzene-sulphonamide, N-[2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-4-methylsulphanyl-benzene-sulphonamide, 1,3-benzodioxol-5-sulphonic acid 2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-ylamide, N-[2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-3,4-dimethoxy-benzene-sulphonamide, N-[2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-2,5-dimethoxy-benzene-sulphonamide, pyridine-3-sulphonic acid 2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-ylamide, 5-methyl-pyridine-2-sulphonic acid 2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-ylamide, 5-isopropyl-pyridine-2-sulphonic acid 2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-ylamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-benzenesulphonamide, 1,3-benzodioxol-5-sulphonic acid 5-(2-

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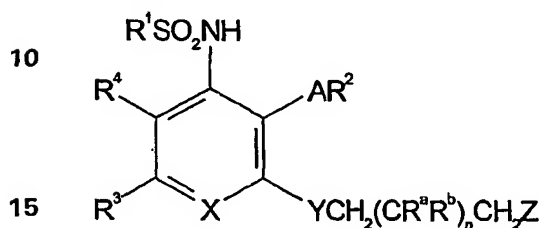
- chloro-5-methoxy-phenoxy)-2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-pyrimidin-4-ylamide, 5-isopropyl-pyridine-2-sulphonic acid 5-(2-chloro-5-methoxy-phenoxy)-2-(2-cyano-pyridin-4-yl)-6-(2-hydroxy-ethoxy)-pyrimidin-4-ylamide, 4-tert-butyl-N-[2-(6-cyano-pyridin-2-yl)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzene-sulphonamide, N-[6-(2-benzyloxy-ethoxy)-2-(2-cyano-pyridin-4-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-4-tert-butyl-benzenesulphonamide, 5-isopropyl-pyridine-2-sulphonic acid-N-[6-(2-benzyloxy-ethoxy)-2-(2-cyanopyridin-4-yl)-5-(2-methoxyphenoxy)-pyrimidin-4-yl]-amide, 4-tert-butyl-N-[2-(2-cyano-pyridin-4-yl)-5-(2-methoxy-phenoxy)-6-(2-tetrahydro-pyran-2-yl)-ethoxy]-pyrimidin-4-yl]-benzenesulphonamide, 4-tert-butyl-N-[2-
- 10 [2-(amino-imino-methyl)-pyridin-4-yl]-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide, 4-tert-butyl-N-[2-[2-(hydroxyamino-imino-methyl)-pyridin-4-yl]-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide, ethyl 4-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine-2-carboxylate, 4-[4-(4-tert-butyl-
- 15 phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine-2-carboxylic acid, 4-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(1-oxy-pyridin-
- 20 4-yl)-pyrimidin-4-yl]-4-methyl-benzene-sulphonamide, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-yl]-4-methoxy-benzene-sulphonamide, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-yl]-4-methoxy-methyl-sulphonamide. 1,3-benzodioxol-5-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-ylamide, N-
- 25 [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-yl]-3,4-dimethoxy-benzene-sulphonamide, N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-yl]-2,5-dimethoxy-benzene-sulphonamide, pyridine-3-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-ylamide, 5-methyl-pyridine-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-
- 30 methoxy-phenoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-ylamide, 5-isopropyl-pyridine-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-ylamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide, 1,3-benzodioxol-4-sulphonic acid 5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-(1-oxy-pyridin-4-

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yl)-pyrimidin-4-ylamide, 5-isopropyl-pyridine-2-sulphonic acid 5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-2-(1-oxy-pyridin-4-yl)-pyrimidin-4-ylamide, 2-[4-(4-tert-butyl-phenylsulphonylamino)-6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine 1-oxide.

5 g. International Patent Application Publication No. WO 96/19455

In particular, compounds of formula I are intended for use in the methods provided herein.



wherein R¹ signifies phenyl, substituted phenyl or heterocyclyl; R² signifies phenyl or substituted phenyl; R³ signifies hydrogen, lower-alkyl, cyano, carboxy, esterified
 20 carboxy, phenyl, substituted phenyl, heterocyclyl or a residue -CONR⁵R⁶ or -NR⁵COR⁷; R⁴ signifies hydrogen or lower-alkyl; R⁵ signifies hydrogen or a residue R⁷, and R⁶ signifies -(CH₂)_mR⁷; or R⁵ and R⁶ together with the N atom associated with them signify a heterocyclic residue; R⁷ signifies phenyl, substituted phenyl, cycloalkyl, hetero-cyclyl, lower-alkyl, cyano-lower-alkyl, hydroxy-lower-alkyl, di-lower-alkylamino-lower-alkyl,
 25 carboxy-lower-alkyl, lower-alkoxycarbonyl-lower-alkyl, lower-alkoxycarbonylamino-lower-alkyl or phenyl-lower-alkoxycarbonyl; R^a signifies hydrogen, lower-alkyl or hydroxy; R^b signifies hydrogen or lower-alkyl; Z signifies hydroxy, amino or a residue -OR⁸, -OC(O)NHR⁸, -OC(O)OR⁸, -NHC(O)NHR⁸ or -NHC(O)OR⁸; R⁸ signifies heterocyclyl, phenyl, substituted phenyl or lower-alkyl; A and Y each independently signify oxygen or
 30 sulphur, X signifies nitrogen or CH; m signifies 0, 1 or 2; and n signifies 0, 1 or 2; and pharmaceutically usable salts thereof.

Preferred compounds of this embodiment include pyridin-2-yl-carbamic acid 2-[3-(4-tert-butyl-benzene-sulphonylamino)-2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[3-(4-tert-butyl-benzene-sulphonylamino-2-(2-methoxy-phenoxy)-5-(2-pyridin-2-yl-ethylcarbamoyl)-phenoxy]-ethyl
 35 ester, pyridin-2-yl-carbamic acid 2-[3-(4-tert-butyl-benzene-sulphonylamino)-2-(2-methoxy-phenoxy)-5-(piperidine-1-carbonyl)-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[5-benzylcarbamoyl-3-(4-tert-butylbenzenesulphonylamino)-2-(2-methoxy-

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- phenoxy)-phenoxy]-ethyl ester, benzyl {3-(4-tert-butyl-benzenesulphonylamino)-4-(2-methoxy-phenoxy)-5-[2-(pyridin-2-ylcarbamoxyloxy)-ethoxy]-benzoylamino}-acetate, pyridin-2-yl-carbamic acid 2-[3-(4-tert-butylbenzene-sulphonylamino)-2-(2-methoxy-phenoxy)-5-[(pyridin-3-yl-methyl)-carbamoxy]-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[3-(4-tert-butyl-benzene-sulphonylamino)-2-(2-methoxy-phenoxy)-5-phenylcarbamoxy]-phenoxy]-ethyl ester, methyl 3-(benzo[1,3]dioxol-5-sulphonylamino)-4-(2-methoxy-phenoxy)-5-[2-(pyridin-2-ylcarbamoxyloxy)-ethoxy]-benzoate, pyridin-2-yl-carbamic acid 2-[3-(benzo[1,3]dioxol-5-sulphonylamino)-2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenoxy]-ethyl ester, ethyl 4-[3-(benzo[1,3]dioxol-5-sulphonylamino)-4-(2-methoxy-phenoxy)-5-[2-(pyridin-2-ylcarbamoxyloxy)-ethoxy]-benzoyl]-piperazine-1-carboxylate, pyridin-2-yl-carbamic acid 2-[3-(benzo[1,3]dioxol-5-sulphonylamino)-5-isobutylcarbamoxy]-2-(2-methoxy-phenoxy)-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[3-(benzo[1,3]dioxol-5-sulphonylamino)-5-isopropylcarbamoxy]-2-(2-methoxy-phenoxy)-phenoxy]-ethyl ester, methyl 3-(4-methoxy-benzenesulphonylamino)-4-(2-methoxy-phenoxy)-5-[2-(pyridin-2-ylcarbamoxyloxy)-ethoxy]-benzoate, pyridin-2-yl-carbamic acid 2-[3-(4-methoxy-benzene-sulphonylamino)-2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenoxy]-ethyl ester, ethyl 4-[4-(2-methoxy-phenoxy)-3-(4-methylsulphonyl-benzenesulphonylamino)-5-[2-(pyridin-2-ylcarbamoxyloxy)-ethoxy]-benzoyl]-piperazine-1-carboxylate, methyl 4-(2-methoxy-phenoxy)-3-[2-(pyridin-2-yl-carbamoxyloxy)-ethoxy]-5-(toluene-4-sulphonylamino)-benzoate, pyridin-2-yl-carbamic acid 2-[2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-3-(toluene-4-sulphonylamino)-phenoxy]-ethyl ester, 3-(4-tert-butyl-benzenesulphonylamino)-4-(2-chloro-5-methoxy-phenoxy)-5-(2-hydroxy-ethoxy)-N-phenyl-benzamide, methyl 3-(4-tert-butyl-benzenesulphonylamino)-4-(2-chloro-5-methoxy-phenoxy)-5-[2-(pyridin-2-ylcarbamoxyloxy)-ethoxy]-benzoate, pyridin-2-yl-carbamic acid 2-[3-(4-tert-butyl-benzene-sulphonylamino)-2-(2-chloro-5-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenoxy]-ethyl ester, methyl 3-(4-tert-butyl-benzenesulphonylamino)-4-(3-methoxy-phenoxy)-5-[2-(pyridin-2-ylcarbamoxyloxy)-ethoxy]-benzoate, pyridin-2-yl-carbamic acid 2-[3-(4-tert-butyl-benzene-sulphonylamino)-2-(3-methoxy-phenoxy)-5-(3-methoxy-phenyl-carbamoxy)-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[3-(4-tert-butyl-benzene-sulphonylamino)-2-(3-methoxy-phenoxy)-5-phenylcarbamoxy]-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[3-(4-methoxy-benzene-sulphonylamino)-2-(3-

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- methoxy-phenoxy)-5-phenylcarbamoyl-phenoxy]-ethyl ester, {3-(4-tert-butyl-benzenesulphonylamino)-4-(2-methoxy-phenoxy)-5-[2-(pyridin-2-ylcarbamoyloxy)-ethoxy]-benzoyl-amino}-acetic acid, pyridin-2-ylcarbamic acid 2-[3-(4-tert-butyl-phenylsulphonylamino)-2-(2-methoxy-phoxy)-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid
- 5 2-[3-(4-tert-butyl-phenylsulphonylamino)-2-(2-chloro-5-methoxy-phenoxy)-ethyl ester, methyl 3-(4-tert-butyl-phenylsulphonyl-amino)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-benzoate, 3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-benzoic acid, 4-tert-butyl-N-[3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenyl]-benzene-sulphonamide, 4-tert-butyl-N-[3-(2-
- 10 hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-5-(piperidine-1-carbonyl)-phenyl]-benzene-sulphonamide, 3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-N-(2-pyridin-2-yl-ethyl)-benzamide, benzyl [3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-benzoylamino]-acetate, 3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-
- 15 phenoxy)-N-phenyl-benzamide, 3-(4-tert-butyl-benzenesulphonyl-amino)-N-cyanomethyl-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-benzamide, 3-(4-tert-butyl-benzenesulphonylamino)-N-(2-dimethylamino-ethyl)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-benzamide, tert-butyl {2-[3-(4-tert-butyl-benzenesulphonylamino)-5-(2-
- 20 hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-benzoylamino]-ethyl}-carbamate, 3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-N-pyridin-3-ylmethyl-benzamide, N-benzyl-3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-benzamide, [3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-benzoylamino]-acetic acid, methyl 3-
- 25 (benzo[1,3]dioxol-5-sulphonylamino)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-benzoate, 3-(benzo[1,3]dioxol-5-sulphonylamino)-5-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-benzoic acid, benzo[1,3]dioxol-5-sulphonic acid [3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenyl]-amide, ethyl N4-[3-
- 30 benzo[1,3]dioxol-5-sulphonylamino)-5-(2-hydroxy-ethoxy)-4-(2-methoxyphenoxy)-benzoyl]-piperazine-1-carboxylate, 3-(benzo[1,3]dioxol-5-sulphonylamino)-5-(2-hydroxy-ethoxy)-N-isobutyl-4-(2-methoxy-phenoxy)-benzamide, 3-(benzo[1,3]dioxol-5-sulphonylamino)-5-(2-hydroxy-ethoxy)-N-isopropyl-4-(2-methoxy-phenoxy)-benzamide, 3-(benzo[1,3]dioxol-5-sulphonylamino)-5-(2-hydroxy-ethoxy)-N-(2-hydroxy-ethyl)-4-(2-methoxy-phenoxy)-benzamide, methyl 3-(2-hydroxy-ethoxy)-5-(4-methoxybenzene-sulphonylamino)-4-(2-methoxy-phenoxy)-benzoate, 3-(2-hydroxy-ethoxy)-5-(4-methoxy-

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- benzenesulphonyl-amino)-4-(2-methoxy-phenoxy)-benzoic acid, N-[3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenyl]-4-methoxy-benzene-sulphonamide, methyl 3-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-5-(4-methylsulphanyl-benzenesulphonylamino)-benzoate, 3-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-5-(4-methylsulphanyl-benzenesulphonylamino)-benzoic acid, N-[3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenyl]-4-methylsulphanyl-benzene-sulphonamide, ethyl 4-[3-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-5-(4-methylsulphanyl-benzenesulphonyl-amino)-benzoyl]-piperazine-1-carboxylate, pyridin-2-yl-carbamic acid 2-[2-(2-methoxy-phenoxy)-3-(4-methylsulphanyl-benzenesulphonylamino)-5-(morpholine-4-carbonyl)-phenoxy]-ethyl ester, methyl 3-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-5-(toluene-4-sulphonylamino)-benzoate, 3-(2-hydroxy-ethoxy)-4-(2-methoxy-phenoxy)-5-(toluene-4-sulphonylamino)-benzoic acid, N-[3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenyl]-4-methyl-benzenesulphonamid, methyl 3-(4-tert-butylbenzenesulphonylamino)-4-(2-chloro-5-methoxy-phenoxy)-5-(2-hydroxy-ethoxy)-benzoate, methyl 3-amino-4-(2-chloro-5-methoxy-phenoxy)-5-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-benzoate, 3-(4-tert-butyl-benzenesulphonylamino)-4-(2-chloro-5-methoxy-phenoxy)-5-(2-hydroxy-ethoxy)-benzoic acid, 4-tert-butyl-N-[2-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-5-(morpholine-4-carbonyl)-phenyl]-benzene-sulphonamide, methyl 4-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-5-(4-methoxy-benzenesulphonylamino)-benzoate, 4-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-5-(4-methoxy-benzenesulphonylamino)-benzoic acid, 4-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-5-(4-methoxy-benzenesulphonylamino)-N-phenyl-benzamide, methyl 3-(benzo[1,3]dioxol-5-sulphonylamino)-4-(2-chloro-5-methoxy-phenoxy)-5-(2-hydroxy-ethoxy)-benzoate, 3-(benzo[1,3]dioxol-5-sulphonylamino)-4-(2-chloro-5-methoxy-phenoxy)-5-(2-hydroxy-ethoxy)-benzoic acid, 3-(benzo[1,3]dioxol-5-sulphonylamino)-4-(2-chloro-5-methoxy-phenoxy)-5-(2-hydroxy-ethoxy)-N-phenyl-benzamide, methyl 4-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-5-(4-trifluoromethyl-benzenesulphonylamino)-benzoate, 4-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-5-(4-trifluoromethyl-benzenesulphonylamino)-benzoic acid, 4-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-N-phenyl-5-(4-trifluoromethyl-benzenesulphonylamino)-benzamide, methyl 3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-benzoate, 3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-benzoic acid, 4-

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- tert-butyl-N-[3-(2-hydroxy-ethoxy)-2-(3-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenyl]-benzene-sulphonamide, 3-(4-tert-butylbenzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-N-phenyl-benzamide, N-biphenyl-2-yl-3-(4-tert-butylbenzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-benzamide, 3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-N-(3-methoxy-phenyl)-benzamide, methyl 2-[3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-benzoylamino]-4-methyl-pentanoate, N-benzo-[1,3]dioxol-5-yl-3-(4-tert-butylbenzene-sulphonylamino)-5-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-benzamide, 2-[3-(4-tert-butyl-benzenesulphonylamino)-5-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-benzoylamino]-4-methyl-pentanoic acid, methyl 3-(2-hydroxy-ethoxy)-5-(4-methoxy-benzene-sulphonylamino)-4-(3-methoxy-phenoxy)-benzoate, 3-(2-hydroxy-ethoxy)-5-(4-methoxy-benzenesulphonyl-amino)-4-(3-methoxy-phenoxy)-benzoic acid, 3-(2-hydroxy-ethoxy)-5-(4-methoxy-benzenesulphonyl-amino)-4-(3-methoxy-phenoxy)-N-phenyl-benzamide, methyl 3-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-5-(4-methylsulphanyl-benzenesulphonylamino)-benzoate, 3-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-5-(4-methylsulphanyl-benzenesulphonylamino)-benzoic acid, 3-(2-hydroxy-ethoxy)-4-(3-methoxy-phenoxy)-5-(4-methylsulphanyl-benzenesulphonyl-amino)-N-phenyl-benzamide, 4-tert-butyl-N-[3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-phenyl]-benzenesulphonamide, 4-tert-butyl-N-[2-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-phenyl]benzenesulphonamide, methyl 3-(4-tert-butylbenzenesulphonylamino)-5-(2,3-dihydroxy-propoxy)-4-(3-methoxy-phenoxy)-benzoate, 3-(4-tert-butyl-benzenesulphonylamino)-5-(2,3-dihydroxy-propoxy)-4-(3-methoxy-phenoxy)-benzoic acid, 3-(4-tert-butyl-benzenesulphonylamino)-5-(2,3-dihydroxy-propoxy)-4-(3-methoxy-phenoxy)-N-phenyl-benzamide, methyl 3-(2,3-dihydroxy-propoxy)-5-(4-methoxy-benzene-sulphonylamino)-4-(3-methoxy-phenoxy)-benzoate, 3-(2,3-dihydroxy-propoxy)-5-(4-methoxy-benzene-sulphonylamino)-4-(3-methoxy-phenoxy)-benzoic acid, 3-(2,3-dihydroxy-propoxy)-5-(4-methoxy-benzene-sulphonylamino)-4-(3-methoxy-phenoxy)-N-phenyl-benzamide, methyl 3-(2,3-dihydroxy-propoxy)-4-(3-methoxy-phenoxy)-5-(4-methylsulphanyl-benzenesulphonylamino)-benzoate, 3-(2,3-dihydroxy-propoxy)-4-(3-methoxy-phenoxy)-5-(4-methylsulphanyl-benzenesulphonylamino)-benzoic acid, 3-(2,3-dihydroxy-propoxy)-4-(3-methoxy-phenoxy)-5-(4-methylsulphanyl-benzenesulphonylamino)-N-phenyl-benzamide, 3-(4-tert-butylbenzenesulphonylamino)-5-(2,3-dihydroxy-propoxy)-4-(3-methoxy-phenoxy)-N-(1H-tetrazol-5-yl)-benzamide, ethyl 4-[3-(2,3-dihydroxy-propoxy)-4-(3-methoxy-phenoxy)-5-

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- (4-methylsulphanylbenzenesulphonylamino)-benzoyl]-piperazine-1-carboxylate, N-[3-(2,3-dihydroxy-propoxy)-2-(3-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenyl]-4-methylsulphanylbenzene-sulphonamide, N-[3-(2-hydroxy-ethoxy)-2-(3-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenyl]-4-methylsulphanyl-benzene-sulphonamide,
- 5 4-tert-butyl-N-[5-cyano-3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-phenyl]-benzenesulphonamide, 4-tert-butyl-N-[3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-5-(1H-tetrazol-5-yl)-phenyl]-benzenesulphonamide, 4-tert-butyl-N-[5-cyano-3-(2-hydroxy-ethoxy)-2-(3-methoxy-phenoxy)-phenyl]-benzenesulphonamide, 4-tert-butyl-N-[3-(2-hydroxy-ethoxy)-2-(3-methoxy-phenoxy)-5-(1H-tetrazol-5-yl)-phenyl]-
- 10 benzenesulphonamide, 4-tert-butyl-N-[5-cyano-3-(2,3-dihydroxy-propoxy)-2-(2-methoxy-phenoxy)-phenyl]-benzenesulphonamide, 4-tert-butyl-N-[3-(2,3-dihydroxy-propoxy)-2-(2-methoxy-phenoxy)-5-(1H-tetrazol-5-yl)-phenyl]-benzenesulphonamide, 4-tert-butyl-N-[5-cyano-3-(2,3-dihydroxy-propoxy)-2-(3-methoxy-phenoxy)-phenyl]-benzenesulphonamide, 4-tert-butyl-N-[3-(2,3-dihydroxy-propoxy)-2-(3-methoxy-phenoxy)-5-(1H-tetrazol-5-yl)-
- 15 phenyl]-benzenesulphonamide, pyridin-2-yl-carbamic acid 2-[3-(5-isopropyl-pyridine-2-sulphonylamino)-2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[3-(5-isopropyl-pyridine-2-sulphonylamino)-2-(2-methoxy-phenoxy)-5-(piperidine-1-carbonyl)-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[3-(5-isopropyl-pyridine-2-sulphonylamino)-2-(2-methoxy-phenoxy)-5-(4-methyl-piperazine-
- 20 1-carbonyl)-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[5-(2,6-dimethyl-morpholine-4-carbonyl)-3-(5-isopropyl-pyridine-2-sulphonyl-amino)-2-(2-methoxy-phenoxy)-phenoxy]-ethyl ester, pyridin-2-yl-carbamic acid 2-[3-(5-isopropyl-pyridine-2-sulphonylamino)-2-(2-methoxy-phenoxy)-5-(2-pyridin-2-ylethylcarbamoxy)-phenoxy]-ethyl ester, ethyl 4-[3-(5-isopropyl-pyridine-2-sulphonylamino)-4-(2-methoxy-phenoxy)-5-[2-
- 25 (pyridin-2-ylcarbamoxyloxy)-ethoxy]-benzoyl]-piperazine-1-carboxylate, pyridin-2-yl-carbamic acid 2-[5-(4-formyl-piperazine-1-carbonyl)-3-(5-isopropyl-pyridine-2-sulphonylamino)-2-(2-methoxy-phenoxy)-phenoxy]-ethyl ester, methyl 4-(2-chloro-5-methoxy-phenoxy)-3-(5-isopropyl-pyridine-2-sulphonylamino)-5-[2-(pyridin-2-ylcarbamoxyloxy)-ethoxy]-benzoate, pyridin-2-yl-carbamic acid 2-[2-(2-chloro-5-methoxy-phenoxy)-3-(5-isopropyl-pyridine-2-sulphonylamino)-5-(morpholine-4-carbonyl)-phenoxy]-
- 30 ethyl ester, pyridin-2-yl carbamic acid 2-[3-(5-isopropyl-pyridyl-sulphonylamino)-2-(2-methoxy-phenoxy)-ethyl ester, methyl 3-(2-hydroxy-ethoxy)-5-(5-isopropyl-pyridine-2-sulphonylamino)-4-(2-methoxy-phenoxy)-benzoate, 3-(2-hydroxy-ethoxy)-5-(5-isopropyl-pyridine-2-sulphonylamino)-4-(2-methoxy-phenoxy)-benzoic acid, 5-isopropyl-pyridine-2-

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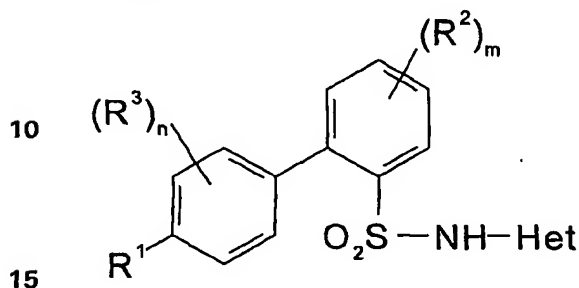
- sulphonic acid [3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-phenyl]-amide, 5-isopropyl-pyridine-2-sulphonic acid [3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-5-(piperidine-1-carbonyl)-phenyl]-amide, 5-isopropyl-pyridine-2-sulphonic acid [3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-5-(4-methyl-piperazine-1-carbonyl)-phenyl]-amide, 5-isopropyl-pyridine-2-sulphonic acid [5-(2,6-dimethyl-morpholine-4-carbonyl)-3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-phenyl]-amide, 3-(2-hydroxy-ethoxy)-5-(5-isopropyl-pyridine-2-sulphonylamino)-4-(2-methoxy-phenoxy)-N-(2-pyridin-2-yl-ethyl)-benzamide, ethyl 4-[3-(2-hydroxyethoxy)-5-(5-isopropyl-pyridine-2-sulphonylamino)-4-(2-methoxy-phenoxy)-benzoyl]-piperazine-1-carboxylate, 5-isopropyl-
- 5 pyridine-2-sulphonic acid [5-(4-formyl-piperazine-1-carbonyl)-3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-phenyl]-amide, 3-(2-hydroxy-ethoxy)-5-(5-isopropyl-pyridine-2-sulphonylamino)-4-(2-methoxy-phenoxy)-N-propylbenzamide, methyl 4-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-5-(5-isopropyl-pyridine-2-sulphonylamino)-benzoate, 4-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-5-(5-isopropyl-pyridine-
- 10 2-sulphonylamino)-benzoic acid, 5-isopropyl-pyridine-2-sulphonic acid [2-(2-chloro-5-methoxy-phenoxy)-3-(2-hydroxy-ethoxy)-5-(morpholine-4-carbonyl)-phenyl]-amide, 5-isopropyl-N-[3-(2-hydroxy-ethoxy)-2-(2-methoxy-phenoxy)-phenyl-pyridyl]-sulphonamide, pyridin-2-yl-carbamic acid 2[4(4-tert-butyl-benzenesulphonamino)-3-(2-methoxyphenoxy)-6-phenyl-pyridin-2-yloxy]-ethyl-ester, p-tert-butyl-N-[2-(2-
- 15 hydroxyethoxy)-3-(o-methoxy-phenoxy)-6-methyl-4-pyridyl]-benzenesulphonamide, p-tert-butyl-N-[2-(2-hydroxyethoxy)-3-(3-methoxy-phenoxy)-6-methyl-4-pyridyl]-benzenesulphonamide, 4-tert-butyl-N-[2-(2-hydroxyethoxy)-3-(2-methoxy-phenoxy)-6-phenyl-pyrid-4-yl]-benzenesulphonamide, Pyridin-2-yl-carbamic acid-2-[4-(5-isopropyl-pyridine-2-sulphonylamino)-3-(2-methoxy-phenoxy)-6-methyl-pyridin-2-yloxy]-
- 20 ethyl ester, methyl 3-(4-tert.-butyl-benzenesulphonylamino)-4-(2-methoxy-phenoxy)-5-[2-(pyrimidin-2-yloxy)-ethoxy]-benzoate, 4-tert-butyl-N-{2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-3-[2-(pyrimidin-2-yloxy)-ethoxy]-phenyl}-benzene-sulphonamide, 4-tert.-butyl-N-{2-(2-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-3-[2-(pyridin-2-yloxy)-ethoxy]-phenyl}-benzene-sulphonamide, 4-(3-methoxy-phenoxy)-3-(4-methylsulphanyl)-
- 25 benzene-sulphonylamino)-N-phenyl-5-[2-(pyrimidin-2-yloxy)-ethoxy]-benzamide, 4-(3-methoxy-phenoxy)-3-(4-methylsulphanyl)-benzene-sulphonylamino)-N-phenyl-5-[2-(pyridin-2-yloxy)-ethoxy]-benzamide, N-[2-(3-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-3-[2-(pyrimidin-2-yloxy)-ethoxy]-phenyl]-4-methylsulphanyl-
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benzenesulphonamide, N-{2-(3-methoxy-phenoxy)-5-(morpholine-4-carbonyl)-3-[2-(pyridin-2-yloxy)-ethoxy]-phenyl}-4-methylsulphonyl-benzenesulphonamide.

h. U.S. Patent No. 5,668,137

Other compounds for use in the methods provided herein include those of the
5 formula:



wherein R^1 is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy or (1-6C)alkylthio, each of which last five groups bear a substituent selected from carboxy, (1-6C)alkoxycarbonyl, carbamoyl, N -(1-6C)alkylcarbamoyl and N,N -di(1-6C)alkylcarbamoyl; R^2 is an optional substituent selected from halogeno, (1-6C)alkyl, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, carbamoyl, N -(1-6C)alkylcarbamoyl, N,N -di(1-6C)alkylcarbamoyl, cyano, amino, N -(1-6C)alkylamino and N,N -di(1-6C)alkylamino; R^3 is an optional substituent selected from (1-6C)alkyl, amino(1-6C)alkyl, hydroxy(1-6C)alkyl, N -[(1-4C)alkylamino(1-6C)alkyl], N,N -[di(1-4C)alkylamino(1-6C)alkyl],
25 carboxy(1-6C)alkyl, (1-6C)alkoxycarbonyl(1-6C)alkyl, carbamoyl(1-6C)alkyl, (1-6C)alkylcarbamoyl(1-6C)alkyl, di(1-6C)alkylcarbamoyl(1-6C)alkyl, carboxy(1-6C)alkoxy, carboxy(1-6C)alkylthio, (1-6C)alkoxycarbonyl(1-6C)alkoxy, (1-6C)alkoxycarbonyl(1-6C)alkylthio, carbamoyl(1-6C)alkoxy, (1-6C)alkylcarbamoyl(1-6C)alkoxy, di(1-6C)alkylcarbamoyl(1-6C)-alkoxy, carbamoyl(1-6C)alkylthio, (1-6C)alkylcarbamoyl(1-6C)alkylthio, di(1-6C)alkylcarbamoyl(1-6C)alkylthio, (2-6C)alkenyl, carboxy(2-6C)alkenyl, (2-6C)alkynyl, carboxy(2-6C)alkynyl, (1-6C)alkoxycarbonyl(2-6C)alkenyl, carbamoyl(2-6C)alkenyl, carbamoyl(2-6C)alkynyl, N -(1-6C)alkylcarbamoyl(2-6C)alkenyl, N,N -di(1-6C)alkylcarbamoyl(2-6C)alkenyl, (1-6C)alkoxycarbonyl(2-6C)alkynyl, carbamoyl(2-6C)alkynyl, N -(1-6C)alkylcarbamoyl(2-6C)alkynyl, N,N -di(1-6C)alkylcarbamoyl(2-6C)alkynyl, halogeno(2-6C)alkyl, trifluoromethyl, trichloromethyl, tribromomethyl, (1-6C)alkoxy, dihalogeno(1-6C)alkoxy, trihalogeno(1-6C)alkoxy, (2-6C)alkenyloxy, (1-4C)alkoxy(1-6C)alkyl, (1-4C)alkylthio(1-6C)alkyl, (1-4C)alkylsulphiny(1-6C)alkyl, (1-4C)alkylsulphonyl(1-6C)alkyl, (1-4C)alkylenedioxy, (3-
35

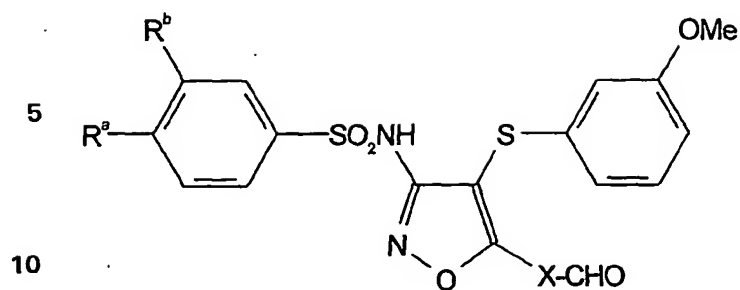
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- 6C)cycloalkyl, (3-8C)cycloalkyl(1-6C)alkyl, phenyl, phenyl(1-6C)alkyl, phenoxy, phenyl(1-6C)alkoxy, halogeno, hydroxy, mercapto, cyano, nitro, carboxy, (1-6C)alkoxycarbonyl, (2-6C)alkenyloxy carbonyl, phenyloxy carbonyl, phenyl(1-6C)alkoxycarbonyl, (1-6C)alkanoyl, benzoyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, (1-6C)alkanoylamino, trifluoroacetyl, trifluoroacetamido, N-[(1-4C)alkyl]trifluoroacetamido, benzamido, N-[(1-4C)alkyl]benzamido, carbamoyl, (1-4C)alkylcarbamoyl, di(1-4C)alkylcarbamoyl, phenylcarbamoyl, sulphamoyl, N-(1-4C)alkylsulphamoyl, N,N-di(1-4C)alkylsulphamoyl, N-phenylsulphamoyl, (1-6C)alkanesulphonamido, benzenesulphonamido, ureido, 3-(1-6C)alkylureido, 3-phenylureido, thioureido, 3-(1-6C)alkylthioureido, 3-phenylthioureido and a group -NRyRz in which Ry and Rz are independently selected from hydrogen, (1-6C)alkyl, phenyl(1-4C)alkyl and (1-6C)alkyl bearing a carboxy, (1-6C)alkoxycarbonyl, carbamoyl, (1-6C)alkylcarbamoyl or di(1-6C)alkylcarbamoyl group, or the group -NRyRz taken together complete a 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 1-piperidinyl or 2-oxo-1-piperidinyl ring; Het is a heterocyclic ring selected from the groups of partial structural formulae IIa, IIb, IIc, IId and IIe set out hereinafter wherein Ra, Rc and Re are individually selected from hydrogen, halogeno, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethoxy; Rb is selected from hydrogen, halogeno, (1-4C)alkyl, methoxy, ethoxy, trifluoromethyl and ethynyl; Rd and Rf are individually selected from halogeno, (1-4C)alkyl, methoxy, ethoxy, trifluoromethyl and ethynyl; Rg is selected from methyl and bromo; Rh is methoxy or ethoxy; m is zero, 1, 2 or 3; n is zero, 1, 2 or 3; and wherein any of said phenyl or benzene moieties of R³ may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or a pharmaceutically-acceptable salt thereof.
- Preferred compounds of this embodiment include 4'-(2-carboxypropyl)-N-(3-methoxy-5-methylpyrazin-2-yl)-2-biphenylsulphonamide, 4'-carboxymethoxy-N-(3-methoxy-5-methylpyrazin-2-yl)-2-biphenylsulphonamide, 4'-(1-carboxy)ethoxy-N-(3-methoxy-5-methylpyrazin-2-yl)-2-biphenylsulphonamide, 4'-(1-carboxy)ethoxy-N-(5-chloro-3-methoxypyrazin-2-yl)-2-biphenylsulphonamide and 4'-(2-carboxy-2-methylpropyl)-N-(3-methoxy-5-methylpyrazin-2-yl)-2-biphenylsulphonamide; or a pharmaceutically-acceptable salt thereof.

i. International Patent Application Publication No. WO 97/11942

In particular, compounds of the following formula and table are intended for use in the methods provided herein:

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	R^a	R^b	X
I-5	H	H	CH_2
I-6	Cl	H	$(\text{CH}_2)_2$
I-7	Me	H	$(\text{CH}_2)_3$
I-8	$(\text{CH}_2)_2\text{CH}(\text{OH})\text{Me}$	H	$(\text{CH}_2)_4$
I-9	$(\text{CH}_2)_2\text{CHClMe}$	H	$(\text{CH}_2)_5$
I-10	$(\text{CH}_2)_2\text{CH}=\text{CH}_2$	H	$(\text{CH}_2)_6$
I-11	$\text{CH}=\text{CHCl}$	H	$\text{CH}=\text{CH}$
I-12	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_2\text{OH}$	H	$\text{CH}=\text{CHCH}_2$
I-13	$\text{C}\equiv\text{CH}$	H	$\text{CH}_2\text{CH}=\text{CH}$
I-14	$\text{CH}_2\text{CHBrC}\equiv\text{CH}$	H	$\text{CH}_2\text{CH}=\text{CHCH}_2$
I-15	OMe	H	$(\text{CH}_2)_2\text{CH}=\text{CH}$
I-16	$\text{OCH}_2\text{CH}_2\text{Br}$	H	$\text{CH}=\text{CH}(\text{CH}_2)_3$
I-17	$\text{O}(\text{CH}_2)_3\text{OH}$	H	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_2$
I-18	Ph	H	$(\text{CH}_2)_2\text{CH-CHCH}_2$
I-19	$\text{C}_6\text{H}_4\text{-p-OMe}$	H	$(\text{CH}_2)_3\text{CH}=\text{CH}$
I-20	$\text{C}_6\text{H}_4\text{-p-Pr}$	H	$\text{CH}=\text{CH}(\text{CH}_2)_4$
I-21	$\text{C}_6\text{H}_4\text{-m-Cl}$	H	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_3$
I-22	$\text{C}_6\text{H}_4\text{-m-OH}$	H	$(\text{CH}_2)_2\text{CH}=\text{CH}(\text{CH}_2)_2$
I-23	H	Cl	$(\text{CH}_2)_3\text{CH}=\text{CHCH}_2$
I-24	Cl	Cl	$(\text{CH}_2)_4\text{CH}=\text{CH}_2$
I-25	Me	Cl	$\text{CH}(\text{Me})\text{CH}_2$
I-26	$(\text{CH}_2)_2\text{CH}(\text{OH})\text{Me}$	Cl	$\text{CH}(\text{Et})\text{CH}_2$

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	R ^a	R ^b	X	
5	I-28	(CH ₂) ₂ CHClMe	Cl	CH(Pr)CH ₂
	I-29	(CH ₂) ₂ CH = CH ₂	Br	CH(Bu)CH ₂
	I-30	CH = CHCl	Br	CH ₂ CH(Me)CH ₂
	I-31	CH ₂ CH = CH(CH ₂) ₂ OH	Br	CH ₂ CH(Et)CH ₂
	I-32	C≡CH	Br	CH ₂ CH(Pr)CH ₂
	I-33	CH ₂ CHBrC≡CH	Br	(CH ₂) ₂ CH(Me)CH ₂
	I-34	CH ₂ CH(OH)(CH ₂) ₂ C≡CH	I	(CH ₂) ₂ CH(Et)CH ₂
	I-35	OMe	I	(CH ₂) ₃ CH(Me)CH ₂
10	I-36	OCH ₂ CH ₂ Br	I	CH ₂
	I-37	O(CH ₂) ₃ OH	I	(CH ₂) ₂
	I-38	Ph	F	(CH ₂) ₃
	I-39	C ₆ H ₄ -p-OMe	F	(CH ₂) ₄
15	I-40	C ₆ H ₄ -p-Pr	F	(CH ₂) ₅
	I-41	C ₆ H ₄ -m-Cl	F	(CH ₂) ₆
	I-42	C ₆ H ₄ -m-OH	F	CH = CH
	I-43	H	Me	CH = CHCH ₂
	I-44	Cl	Et	CH ₂ CH = CH
20	I-45	Me	Pr	CH = CH(CH ₂) ₂
	I-46	(CH ₂) ₂ CH(OH)Me	Bu	CH ₂ CH = CHCH ₂
	I-47	(CH ₂) ₂ CHClMe	Me	(CH ₂) ₂ CH = CH
	I-48	(CH ₂) ₂ CH = CH ₂	Et	CH = CH(CH ₂) ₃
	I-49	CH = CHCl	Pr	CH ₂ CH = CH(CH ₂) ₂
	I-50	CH ₂ CH = CH(CH ₂) ₂ OH	Bu	(CH ₂) ₂ CH = CHCH ₂
	I-51	C≡CH	Me	(CH ₂) ₃ CH = CH
	I-52	CH ₂ CHBrC≡CH	Et	CH = CH(CH ₂) ₄
25	I-53	CH ₂ CH(OH)(CH ₂) ₂ C≡CH	Pr	CH ₂ CH = CH(CH ₂) ₃
	I-54	OMe	Bu	(CH ₂) ₂ CH = CH = CH(CH ₂) ₂
	I-55	OCH ₂ CH ₂ Br	Me	(CH ₂) ₃ CH = CHCH ₂
	I-56	O(CH ₂) ₃ OH	Et	(CH ₂) ₄ CH = CH ₂

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	R ^a	R ^b	X
	Ph	Pr	CH(Me)CH ₂
	C ₆ H ₄ -p-Ome	Bu	CH(Et)CH ₂
	C ₆ H ₄ -p-Pr	Me	CH(Pr)CH ₂
	C ₆ H ₄ -m-Cl	Et	CH(Bu)CH ₂
5	I-61 C ₆ H ₄ -m-OH	Pr	CH ₂ CH(Me)CH ₂
	I-62 H	OMe	CH ₂ CH(Et)CH ₂
	I-63 Cl	OEt	CH ₂ CH(Pr)CH ₂
	I-64 Me	OPr	(CH ₂) ₂ CH(Me)CH ₂
	I-65 (CH ₂) ₂ CH(OH)Me	OBu	(CH ₂) ₂ CH(Et)CH ₂
10	I-66 (CH ₂) ₂ CHClMe	OMe	(CH ₂) ₃ CH(Me)CH ₂
	I-67 (CH ₂) ₂ CH=CH ₂	OEt	CH ₂
	I-68 CH=CHCl	OPr	(CH ₂) ₂
	I-69 CH ₂ CH=CH(CH ₂) ₂ OH	OBu	(CH ₂) ₃
	I-70 C≡CH	OMe	(CH ₂) ₄
15	I-71 CH ₂ CHBrC≡CH	OEt	(CH ₂) ₅
	I-72 CH ₂ CH(OH)(CH ₂) ₂ C≡CH	OPr	(CH ₂) ₆
	I-73 OMe	OBu	CH=CH
	I-74 OCH ₂ CH ₂ Br	OMe	CH=CHCH ₂
	I-75 O(CH ₂) ₃ OH	OEt	CH ₂ CH=CH
20	I-76 Ph	OPr	CH=CH(CH ₂) ₂
	I-77 C ₆ H ₄ -p-OMe	OBu	CH ₂ CH=CHCH ₂
	I-78 C ₆ H ₄ -p-Pr	OMe	(CH ₂) ₂ CH=CH
	I-79 C ₆ H ₄ -m-Cl	OEt	CH=CH(CH ₂) ₃
	I-80 C ₆ H ₄ -m-OH	OPr	CH ₂ CH=CH(CH ₂) ₂
25	I-81 H	H	(CH ₂) ₂ CH=CHCH ₂
	I-82 H	Cl	(CH ₂) ₃ CH=CH
	I-83 H	Me	CH=CH(CH ₂) ₄

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	R _a	R _b	X	
5	I-84	H	(CH ₂) ₂ CH(OH)Me	CH ₂ CH = CH(CH ₂) ₃
	I-85	H	(CH ₂) ₂ CHClMe	(CH ₂) ₂ CH = CH(CH ₂) ₂
	I-86	H	(CH ₂) ₂ CH = CH ₂	(CH ₂) ₃ CH = CHCH ₂
	I-87	H	CH = CHCl	(CH ₂) ₄ CH = CH ₂
	I-88	H	CH ₂ CH = CH(CH ₂) ₂ OH	CH(Me)CH ₂
	I-89	H	C≡CH	CH(Et)CH ₂
	I-90	H	CH ₂ CHBrC≡CH	CH(Pr)CH ₂
	I-91	H	CH ₂ CH(OH)(CH ₂) ₂ C≡CH	CH(Bu)CH ₂
10	I-92	H	OMe	CH ₂ CH(Me)CH ₂
	I-93	H	OCH ₂ CH ₂ Br	CH ₂ CH(Et)CH ₂
	I-94	H	O(CH ₂) ₃ OH	CH ₂ CH(Pr)CH ₂
	I-95	H	Ph	(CH ₂) ₂ CH(Me)CH ₂
	I-96	H	C ₆ H ₄ -p-OMe	(CH ₂) ₂ CH(Et)CH ₂
15	I-97	H	C ₆ H ₄ -p-Pr	(CH ₂) ₃ CH(Me)CH ₂
	I-98	H	C ₆ H ₄ -m-Cl	CH ₂
	I-99	H	C ₆ H ₄ -m-OH	(CH ₂) ₂
	I-100	Cl	H	(CH ₂) ₃
20	I-101	Cl	Cl	(CH ₂) ₄
	I-102	Cl	Me	(CH ₂) ₅
	I-103	Cl	(CH ₂) ₂ CH(OH)Me	(CH ₂) ₆
	I-104	Cl	(CH ₂) ₂ CHClMe	CH = CH
	I-105	Br	(CH ₂) ₂ CH = CH ₂	CH = CHCH ₂
	I-106	Br	CH = CHCl	CH ₂ CH = CH
25	I-107	Br	CH ₂ CH = CH(CH ₂) ₂ OH	CH = CH(CH ₂) ₂
	I-108	Br	C≡CH	CH ₂ CH = CHCH ₂
	I-109	Br	CH ₂ CHBrC≡CH	(CH ₂) ₂ CH = CH
	I-110	I	CH ₂ CH(OH)(CH ₂) ₂ C≡CH	CH≡CH(CH ₂) ₃
	I-111	I	OMe	CH ₂ CH = CH(CH ₂) ₂

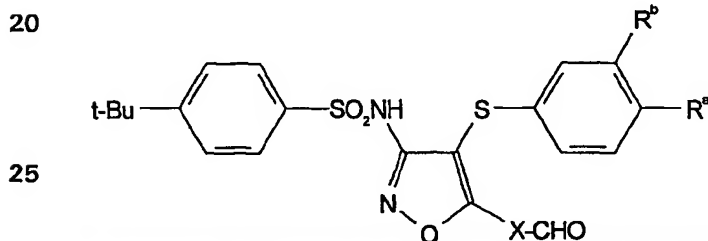
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		R _a	R _b	X
5	I-112	I	OCH ₂ CH ₂ Br	(CH ₂) ₂ CH = CHCH ₂
	I-113	I	O(CH ₂) ₃ OH	(CH ₂) ₃ CH = CH
	I-114	F	Ph	CH = CH(CH ₂) ₄
	I-115	F	C ₆ H ₄ -p-OMe	CH ₂ CH = CH(CH ₂) ₃
	I-116	F	C ₆ H ₄ -p-Pr	(CH ₂) ₂ CH = CH(CH ₂) ₂
	I-117	F	C ₆ H ₄ -m-Cl	(CH ₂) ₃ CH = CHCH ₂
	I-118	F	C ₆ H ₄ -m-OH	(CH ₂) ₄ CH = CH ₂
	I-119	Me	H	CH(Me)CH ₂
10	I-120	Et	Cl	CH(Et)CH ₂
	I-121	Pr	Me	CH(Pr)CH ₂
	I-122	Bu	(CH ₂) ₂ CH(OH)Me	CH(Bu)CH ₂
	I-123	Me	(CH ₂) ₂ CHClMe	CH ₂ CH(Me)CH ₂
15	I-124	Et	(CH ₂) ₂ CH = CH ₂	CH ₂ CH(ET)CH ₂
	I-125	Pr	CH = CHCl	CH ₂ CH(Pr)CH ₂
	I-126	Bu	CH ₂ Ch = CH(CH ₂) ₂ OH	(CH ₂) ₂ CH(Me)CH ₂
	I-127	Me	C≡CH	(CH ₂) ₂ CH(Et)CH ₂
	I-128	Et	CH ₂ CHBrC≡CH	(CH ₂) ₃ CH(Me)CH ₂
	I-129	Pr	CH ₂ CH(OH)(CH ₂) ₂ C≡CH	CH ₂
	I-130	Bu	OMe	(CH ₂) ₂
	20	I-131	Me	OCH ₂ CH ₂ Br
I-132		Et	O(CH ₂) ₃ OH	(CH ₂) ₄
I-133		Pr	Ph	(CH ₂) ₅
I-134		Bu	C ₆ H ₄ -p-OMe	(CH ₂) ₆
25	I-135	Me	C ₆ H ₄ -p-Pr	CH = CH
	I-136	Et	C ₆ H ₄ -m-Cl	CH = CHCH ₂
	I-138	OMe	H	CH = CH(CH ₂) ₂
	I-139	OEt	Cl	CH ₂ CH = CHCH ₂
	I-140	OPr	Me	(CH ₂) ₂ CH = CH
	I-141	OBu	(CH ₂) ₂ CH(OH)Me	CH = CH(CH ₂) ₃

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	R_a	R_b	X	
5	I-142	OMe	$(CH_2)_2CHClMe$	$CH_2Ch = CH(CH_2)_2$
	I-143	OEt	$(CH_2)_2CH = CH_2$	$(CH_2)_2CH = CHCH_2$
	I-144	OPr	$CH = CHCl$	$(CH_2)_3CH = CH$
	I-145	OBu	$CH_2CH = CH(CH_2)_2OH$	$CH = CH(CH_2)_4$
	I-146	OMe	$C \equiv CH$	$CH_2CH = CH(CH_2)_3$
	I-147	OEt	$CH_2CHBrC \equiv CH$	$(CH_2)_2CH = CH(CH_2)_2$
	I-48	OPr	$CH_2CH(OH)(CH_2)_2C \equiv CH$	$(CH_2)_3CH = CHCH_2$
	I-149	OBu	OMe	$(CH_2)_4CH = CH_2$
10	I-150	OMe	OCH_2CH_2Br	$CH(Me)CH_2$
	I-151	OEt	$O(CH_2)_3OH$	$CH(Et)CH_2$
	I-152	OPr	Ph	$CH(Pr)CH_2$
	I-153	OBu	$C_6H_4\text{-}p\text{-OMe}$	$CH(Bu)CH_2$
	I-154	OMe	$C_6H_4\text{-}p\text{-Pr}$	$CH_2CH(Me)CH_2$
15	I-155	OEt	$C_6H_4\text{-}m\text{-Cl}$	$CH_2CH(Et)CH_2$
	I-156	OPr	$C_6H_4\text{-}m\text{-OH}$	$CH_2CH(Pr)CH_2$

Other compounds of this embodiment include those of the following formula and table:



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	R^a	R^b	X
I-157	H	H	CH_2
I-158	Cl	H	$(CH_2)_2$
I-159	Me	H	$(CH_2)_3$
I-160	$(CH_2)_2CH(OH)Me$	H	$(CH_2)_4$

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5	I-161	$(\text{CH}_2)_2\text{CHClMe}$	H	$(\text{CH}_2)_5$
	I-162	$(\text{CH}_2)_2\text{CH}=\text{CH}_2$	H	$(\text{CH}_2)_6$
	I-163	$\text{CH}=\text{CHCl}$	H	$\text{CH}=\text{CH}$
	I-164	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_2\text{OH}$	H	$\text{CH}=\text{CH}_2\text{CH}$
	I-165	$\text{C}\equiv\text{CH}$	H	$\text{CH}_2\text{CH}=\text{CH}$
10	I-166	$\text{CH}_2\text{CHBrC}\equiv\text{CH}$	H	$\text{CH}=\text{CH}(\text{CH}_2)_2$
	I-167	$\text{CH}_2\text{CH}(\text{OH})(\text{CH}_2)_2\text{C}\equiv\text{CH}$	H	$\text{CH}_2\text{CH}=\text{CHCH}_2$
	I-168	OMe	H	$(\text{CH}_2)_2\text{CH}=\text{CH}$
	I-169	$\text{OCH}_2\text{CH}_2\text{Br}$	H	$\text{CH}=\text{CH}(\text{CH}_2)_2$
	I-170	$\text{O}(\text{CH}_2)_3\text{OH}$	H	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_2$
15	I-171	Ph	H	$(\text{CH}_2)_2\text{CH}=\text{CHCH}_2$
	I-172	$\text{C}_6\text{H}_4\text{-p-OMe}$	H	$(\text{CH}_2)_3\text{CH}=\text{CH}$
	I-173	$\text{C}_6\text{H}_4\text{-p-Pr}$	H	$\text{CH}=\text{CH}(\text{CH}_2)_4$
	I-174	$\text{C}_6\text{H}_4\text{-m-Cl}$	H	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_3$
	I-175	$\text{C}_6\text{H}_4\text{-m-OH}$	H	$(\text{CH}_2)_2\text{CH}=\text{CH}(\text{CH}_2)_2$
20	I-176	H	Cl	$(\text{CH}_2)_3\text{CH}=\text{CHCH}_2$
	I-177	Cl	Cl	$(\text{CH}_2)_4\text{CH}=\text{CH}$
	I-178	Me	Cl	$\text{CH}(\text{Me})\text{CH}_2$
	I-179	$(\text{CH}_2)_2\text{CH}(\text{OH})\text{Me}$	Cl	$\text{CH}(\text{Et})\text{CH}_2$
	I-180	$(\text{CH}_2)_2\text{CHClMe}$	Cl	$\text{CH}(\text{Pr})\text{CH}_2$
25	I-181	$(\text{CH}_2)_2\text{CH}=\text{CH}_2$	Br	$\text{CH}(\text{Bu})\text{CH}_2$
	I-182	$\text{CH}=\text{CHCl}$	Br	$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2$
	I-183	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_2\text{OH}$	Br	$\text{CH}_2\text{CH}(\text{Et})\text{CH}_2$
	I-184	$\text{C}\equiv\text{CH}$	Br	$\text{CH}_2\text{CH}(\text{Pr})\text{CH}_2$
	I-185	$\text{CH}_2\text{CHBrC}\equiv\text{CH}$	Br	$(\text{CH}_2)_2\text{CH}(\text{Me})\text{CH}_2$
30	I-186	$\text{CH}_2\text{CH}(\text{OH})(\text{CH}_2)_2\text{C}\equiv\text{CH}$	I	$(\text{CH}_2)_2\text{CH}(\text{Et})\text{CH}_2$
	I-187	OMe	I	$(\text{CH}_2)_3\text{CH}(\text{Me})\text{CH}_2$
	I-188	$\text{OCH}_2\text{CH}_2\text{Br}$	I	CH_2
	I-189	$\text{O}(\text{CH}_2)_3\text{OH}$	I	$(\text{CH}_2)_2$
	I-190	Ph	F	$(\text{CH}_2)_3$

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5	I-191	C ₆ H ₄ -p-OMe	F	(CH ₂) ₄
	I-192	C ₆ H ₄ -p-Pr	F	(CH ₂) ₅
	I-193	C ₆ H ₄ -m-Cl	F	(CH ₂) ₆
	I-194	C ₆ H ₄ -m-OH	F	CH=CH
	I-195	H	Me	CH=CHCH ₂
10	I-196	Cl	Et	CH ₂ CH=CH
	I-197	Me	Pr	CH=CH(CH ₂) ₂
	I-198	(CH ₂) ₂ CH(OH)Me	Bu	CH ₂ CH=CHCH
	I-199	(CH ₂) ₂ CHClMe	Me	(CH ₂) ₂ CH=CH
	I-200	(CH ₂) ₂ CH=CH ₂	Et	CH=CH(CH ₂) ₃
15	I-201	CH=CHCl	Pr	CH ₂ CH=CH(CH ₂) ₂
	I-202	CH ₂ CH=CH(CH ₂) ₂ OH	Bu	(CH ₂) ₂ CH=CHCH ₂
	I-203	C≡CH	Me	(CH ₂) ₃ CH=CH
	I-204	CH ₂ CHBrC≡CH	Et	CH=CH(CH ₂) ₄
	I-205	CH ₂ CH(OH)CH ₂) ₂ C≡CH	Pr	CH ₂ CH=CH(CH ₂) ₃
20	I-206	OMe	Bu	(CH ₂) ₂ CH=CH(CH ₂) ₂
	I-207	OCH ₂ CH ₂ Br	Me	(CH ₂) ₃ CH=CHCH ₂
	I-208	O(CH ₂) ₃ OH	Et	(CH ₂) ₄ CH=CH
	I-209	Ph	Pr	CH(Me)CH ₂
	I-210	C ₆ H ₄ -p-OMe	Bu	CH(Et)CH ₂
25	I-211	C ₆ H ₄ -p-Pr	Me	CH(Pr)CH ₂
	I-212	C ₆ H ₄ -m-Cl	Et	CH(Bu)CH ₂
	I-213	C ₆ H ₄ -m-OH	Pr	CH ₂ CH(Me)CH ₂
	I-214	H	OMe	CH ₂ CH(Et)CH ₂
	I-215	Cl	OEt	CH ₂ CH(Pr)CH ₂
30	I-216	Me	OPr	(CH ₂) ₂ CH(Me)CH ₂
	I-217	(CH ₂) ₂ CH(OH)Me	OBu	(CH ₂) ₂ CH(Et)CH ₂
	I-218	(CH ₂) ₂ CHClMe	OMe	(CH ₂) ₃ CH(Me)CH ₂
	I-219	(CH ₂) ₂ CH=CH ₂	OEt	CH ₂
	I-220	CH=CHCl	OPr	(CH ₂) ₂

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5	I-221	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_2\text{OH}$	OBu	$(\text{CH}_2)_3$
	I-222	$\text{C}\equiv\text{CH}$	OMe	$(\text{CH}_2)_4$
	I-223	$\text{CH}_2\text{CHBrC}\equiv\text{CH}$	OEt	$(\text{CH}_2)_5$
	I-224	$\text{CH}_2\text{CH}(\text{OH})(\text{CH}_2)_2\text{C}\equiv\text{CH}$	OPr	$(\text{CH}_2)_6$
	I-225	OMe	OBu	$\text{CH}=\text{CH}$
10	I-226	$\text{OCH}_2\text{CH}_2\text{Br}$	OMe	$\text{CH}=\text{CHCH}_2$
	I-227	$\text{O}(\text{CH}_2)_3\text{OH}$	OEt	$\text{CH}_2\text{CH}=\text{CH}$
	I-228	Ph	OPr	$\text{CH}=\text{CH}(\text{CH}_2)_2$
	I-229	$\text{C}_6\text{H}_4\text{-p-OMe}$	OBu	$\text{CH}_2\text{CH}=\text{CHCH}_2$
	I-230	$\text{C}_6\text{H}_4\text{-p-Pr}$	OMe	$(\text{CH}_2)_2\text{CH}=\text{CH}$
15	I-231	$\text{C}_6\text{H}_4\text{-m-Cl}$	OEt	$\text{CH}=\text{CH}(\text{CH}_2)_3$
	I-232	$\text{C}_6\text{H}_4\text{-m-OH}$	OPr	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_2$
	I-233	H	H	$(\text{CH}_2)_2\text{CH}=\text{CHCH}_2$
	I-234	H	Cl	$(\text{CH}_2)_3\text{CH}=\text{CH}$
	I-235	H	Me	$\text{CH}=\text{CH}(\text{CH}_2)_4$
20		R_a	R_b	X
	I-236	H	$(\text{CH}_2)_2\text{CH}(\text{OH})\text{Me}$	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_3$
	I-237	H	$(\text{CH}_2)_2\text{CHClMe}$	$(\text{CH}_2)_2\text{CH}=\text{CH}(\text{CH}_2)_2$
	I-238	H	$(\text{CH}_2)_2\text{CH}=\text{CH}_2$	$(\text{CH}_2)_3\text{CH}=\text{CHCH}_2$
	I-239	H	$\text{CH}=\text{CHCl}$	$(\text{CH}_2)_4\text{CH}=\text{CH}$
25	I-240	H	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{OH}$	$\text{CH}(\text{Me})\text{CH}_2$
	I-241	H	$\text{C}\equiv\text{CH}$	$\text{CH}(\text{Et})\text{CH}_2$
	I-242	H	$\text{CH}_2\text{CHBrC}\equiv\text{CH}$	$\text{CH}(\text{Pr})\text{CH}_2$
	I-243	H	$\text{CH}_2\text{CH}(\text{OH})(\text{CH}_2)_2\text{C}\equiv\text{CH}$	$\text{CH}(\text{Bu})\text{CH}_2$
	I-244	H	OMe	$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2$
30	I-245	H	$\text{OCH}_2\text{CH}_2\text{Br}$	$\text{CH}_2\text{CH}(\text{Et})\text{CH}_2$
	I-246	H	$\text{O}(\text{CH}_2)_3\text{OH}$	$\text{CH}_2\text{CH}(\text{Pr})\text{CH}_2$
	I-247	H	Ph	$(\text{CH}_2)_2\text{CH}(\text{Me})\text{CH}_2$
	I-248	H	$\text{C}_6\text{H}_4\text{-p-OMe}$	$(\text{CH}_2)_2\text{CH}(\text{Et})\text{CH}_2$
	I-249	H	$\text{C}_6\text{H}_4\text{-p-Pr}$	$(\text{CH}_2)_3\text{CH}(\text{Me})\text{CH}_2$

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5	I-250	H	C_6H_4 -m-Cl	CH_2
	I-251	H	C_6H_4 -m-OH	$(CH_2)_2$
	I-252	Cl	H	$(CH_2)_3$
	I-253	Cl	Cl	$(CH_2)_4$
	I-254	Cl	Me	$(CH_2)_5$
10	I-255	Cl	$(CH_2)_2CH(OH)Me$	$(CH_2)_6$
	I-256	Cl	$(CH_2)_2CHClMe$	$CH=CH$
	I-257	Br	$(CH_2)_2CH=CH_2$	$CH=CHCH_2$
	I-258	Br	$CH-CHCl$	$CH_2CH=CH$
	I-259	Br	$CH_2CH=CH(CH_2)_2OH$	$CH=CH(CH_2)_2$
15	I-260	Br	$C\equiv CH$	$CH_2CH=CHCH$
	I-261	Br	$CH_2CHBrC\equiv CH$	$(CH_2)_2CH=CH$
	I-262	I	$CH_2CH(OH(CH_2)_2C\equiv CH$	$CH=CH(CH_2)_3$
	I-263	I	OMe	$CH_2CH=CH(CH_2)_2$
	I-264	I	OCH_2CH_2Br	$(CH_2)_2CH=CHCH_2$
20	I-265	I	$O(CH_2)_3OH$	$(CH_2)_3CH=CH$
	I-266	F	Ph	$CH=CH(CH_2)_4$
	I-267	F	C_6H_4 -p-OMe	$CH_2CH=CH(CH_2)_3$
	I-268	F	C_6H_4 -p-Pr	$(CH_2)_2CH=CH(CH_2)_2$
	I-269	F	C_6H_4 -m-Cl	$(CH_2)_3CH=CHCH_2$
25	I-270	F	C_6H_4 -m-OH	$(CH_2)_4CH=CH$
	I-271	Me	H	$CH(Me)CH_2$
	I-272	Et	Cl	$CH(Et)CH_2$
	I-273	Pr	Me	$CH(Pr)CH_2$
	I-274	Bu	$(CH_2)_2CH(OH)Me$	$CH(Bu)CH_2$
30	I-275	Me	$(CH_2)_2CHClMe$	$CH_2CH(Me)CH_2$
	I-276	Et	$(CH_2)_2CH=CH_2$	$CH_2CH(Et)CH_2$
	I-277	Pr	$CH=CHCl$	$CH_2CH(Pr)CH_2$
	I-278	Bu	$CH_2CH=CH(CH_2)_2OH$	$(CH_2)_2CH(Me)CH_2$
	I-279	Me	$C\equiv CH$	$(CH_2)_2CH(Et)CH_2$

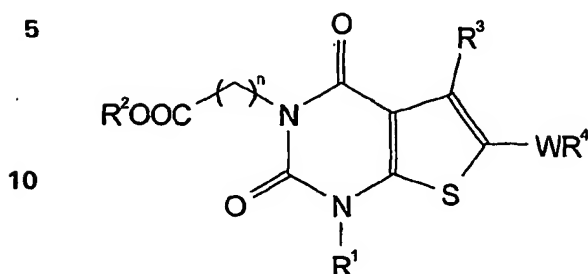
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5	I-280	Et	$\text{CH}_2\text{CHBrC}\equiv\text{CH}$	$(\text{CH}_2)_3\text{CH}(\text{Me})\text{CH}_2$
	I-281	Pr	$\text{CH}_2\text{CH}(\text{OH})\text{CH}_2)_2\text{C}\equiv\text{CH}$	CH_2
	I-282	Bu	OMe	$(\text{CH}_2)_2$
	I-283	Me	$\text{OCH}_2\text{CH}_2\text{Br}$	$(\text{CH}_2)_3$
	I-284	Et	$\text{O}(\text{CH}_2)_3\text{OH}$	$(\text{CH}_2)_4$
10	I-285	Pr	Ph	$(\text{CH}_2)_6$
	I-286	Bu	$\text{C}_6\text{H}_4\text{-p-OMe}$	$(\text{CH}_2)_6$
	I-287	Me	$\text{C}_6\text{H}_4\text{-p-Pr}$	$\text{CH}=\text{CH}$
	I-288	Et	$\text{C}_6\text{H}_4\text{-m-Cl}$	$\text{CH}=\text{CHCH}_2$
	I-289	Pr	$\text{C}_6\text{H}_4\text{-m-OH}$	$\text{CH}_2\text{CH}=\text{CH}$
15	I-290	OMe	H	$\text{CH}=\text{CH}(\text{CH}_2)_2$
	I-291	OEt	Cl	$\text{CH}_2\text{CH}=\text{CHCH}_2$
	I-292	OPr	Me	$(\text{CH}_2)_2\text{CH}=\text{CH}$
	I-293	OBu	$(\text{CH}_2)_2\text{CH}(\text{OH})\text{Me}$	$\text{CH}=\text{CH}(\text{CH}_2)_3$
	I-294	OMe	$(\text{CH}_2)_2\text{CHClMe}$	$\text{CH}_2\text{HC}=\text{CH}(\text{CH}_2)_2$
20	I-295	OEt	$(\text{CH}_2)_2\text{CH}=\text{CH}_2$	$(\text{CH}_2)_2\text{CH}=\text{CHCH}_2$
	I-296	OPr	$\text{CH}=\text{CHCl}$	$(\text{CH}_2)_3\text{CH}=\text{CH}$
	I-297	OBu	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_2\text{OH}$	$\text{CH}=\text{CH}(\text{CH}_2)_4$
	I-298	OMe	$\text{C}\equiv\text{CH}$	$\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_3$
	I-299	OEt	$\text{CH}_2\text{CHBrC}\equiv\text{CH}$	$(\text{CH}_2)_2\text{CH}=\text{CH}(\text{CH}_2)_2$
25	I-300	Opr	$\text{CH}_2\text{CH}(\text{OH}(\text{CH}_2)_2\text{C}\equiv\text{CH})$	$(\text{CH}_2)_3\text{CH}=\text{CHCH}_2$
	I-301	OBu	OMe	$(\text{CH}_2)_4\text{CH}=\text{CH}$
	I-302	OMe	$\text{OCH}_2\text{CH}_2\text{Br}$	$\text{CH}(\text{Me})\text{CH}_2$
	I-303	OEt	$\text{O}(\text{CH}_2)_3\text{OH}$	$\text{CH}(\text{Et})\text{CH}_2$
	I-304	OPr	Ph	$\text{CH}(\text{Pr})\text{CH}_2$
30	I-305	OBu	$\text{C}_6\text{H}_4\text{-p-OMe}$	$\text{CH}(\text{Bu})\text{CH}_2$
	I-306	OMe	$\text{C}_6\text{H}_4\text{-p-Pr}$	$\text{CH}_2\text{CH}(\text{Me})\text{CH}_2$
	I-307	OEt	$\text{C}_6\text{H}_4\text{-m-Cl}$	$\text{CH}_2\text{CH}(\text{Et})\text{CH}_2$
	I-308	OPr	$\text{C}_6\text{H}_4\text{-m-OH}$	$\text{CH}_2\text{CH}(\text{Pr})\text{CH}_2$

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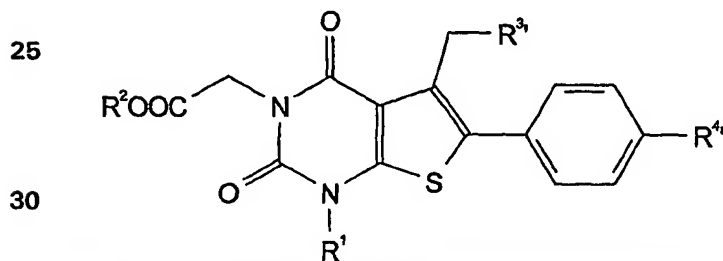
j. International Patent Application Publication No. WO 97/07119

Of particular interest for use in the methods provided herein are compounds of the formula:



- 15 wherein each of R¹ and R² are hydrogen or an optionally substituted hydrocarbon residue, R³ is a C₁₋₆ alkyl group which is substituted by a C₁₋₆ alkoxy-carbonyl group or a group of the formula: -NH-SO₂-R⁵ wherein R⁵ is (1) a C₁₋₆ alkyl group which may optionally be substituted by halogen or (2) a C₆₋₁₄ aryl group, R⁴ is an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group, W
- 20 denotes a chemical bond or a spacer group and n denotes an integer of 1 to 3, or a salt thereof.

Preferred compounds of this embodiment are shown in the following table.



35

Compound No.	R¹	R²	R³	R⁴
1	2-methylthio-benzyl	ethyl	methane-sulfonamido	methoxymethoxy
2	2-methylthio-benzyl	ethyl	benzene-sulfonamido	methoxymethoxy
3(1)	2-methylthio-benzyl	ethyl	methane-sulfonamido	methoxy
3(2)	2-chloro-6-fluorobenzyl	ethyl	methane-sulfonamido	methoxy

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Compound No.	R ¹	R ²	R ³	R ⁴
3(3)	2-chloro-6-fluorobenzyl	ethyl	methane-sulfonamido	isobutoxy
3(4)	2-methylthio-benzyl	ethyl	methane-sulfonamido	propoxy
3(5)	2-methylthio-benzyl	ethyl	ethane-sulfonamido	methoxymethoxy
3(6)	2-methylthio-benzyl	ethyl	propane-sulfonamido	methoxymethoxy
5 3(7)	2-methylthio-benzyl	ethyl	isopropane-sulfonamido	propoxy
3(8)	2-methylthio-benzyl	ethyl	trifluoro-methane-sulfonamido	methoxymethoxy
3(9)	2-methylthio-benzyl	ethyl	isopropane-sulfonamido	methoxymethoxy
3(10)	2-methylthio-benzyl	ethyl	ethane-sulfonamido	propoxy
3(11)	2-methylthio-benzyl	ethyl	methane-sulfonamido	2-methoxyethyl
10 4	2-methylthio-benzyl	ethyl	ethoxy-carbonyl	methoxy
5	2-methylthio-benzyl	H	methane-sulfonamido	methoxymethoxy
6	2-methylthio-benzyl	ethyl	methane-sulfonamido	isobutoxy
7(1)	2-methylthio-benzyl	ethyl	methane-sulfonamido	carboxymethoxy
7(2)	2-methylthio-benzyl	ethyl	methane-sulfonamido	allyloxy
15 7(3)	2-methylthio-benzyl	ethyl	methane-sulfonamido	butoxy
7(4)	2-methylthio-benzyl	ethyl	methane-sulfonamido	2,2,2-trifluoro-ethoxy
8	2-methylthio-benzyl	ethyl	methane-sulfonamido	methylamino-carbonylmethoxy

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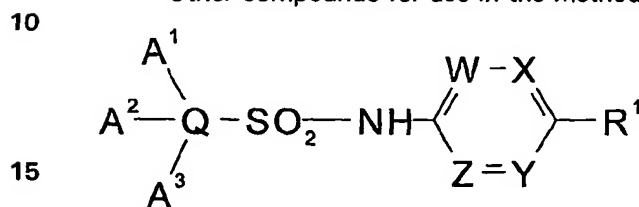
Compound No.	R ¹	R ²	R ³	R ⁴	
9(1)	2-methylthio-benzyl	ethyl	methane-sulfonamido	propylamino-carbonylmethoxy	
9(2)	2-methylthio-benzyl	ethyl	methane-sulfonamido	piperazine-carbonylmethoxy	
10(1)	2-methylthio-benzyl	pivaloyloxy-methyl	methane-sulfonamido	methoxymethoxy	
10(2)	2-methylthio-benzyl	1-(cyclo-hexyloxy-carbonyloxy)-ethyl	methane-sulfonamido	methoxymethoxy	
5	11(1)	2-methylthio-benzyl	H	benzen-sulfonamido	methoxymethoxy
	11(2)	2-methylthio-benzyl	H	methane-sulfonamido	methoxy
	11(3)	2-methylthio-benzyl	ethyl	carboxy	methoxy
	11(4)	2-chloro-6-fluorobenzyl	H	methane-sulfonamido	methoxy
	11(5)	2-chloro-6-fluorobenzyl	H	methane-sulfonamido	isobutoxy
10	11(6)	2-methylthio-benzyl	H	methane-sulfonamido	isobutoxy
	11(7)	2-methylthio-benzyl	H	methane-sulfonamido	propoxy
	11(8)	2-methylthio-benzyl	H	methane-sulfonamido	butoxy
	11(9)	2-methylthio-benzyl	H	ethane-sulfonamido	propoxy
	11(10)	2-methylthio-benzyl	H	methane-sulfonamido	2-methoxyethyl
15	11(11)	2-methylthio-benzyl	H	isopropane-sulfonamido	methoxymethoxy
	11(12)	2-methylthio-benzyl	H	methane-sulfonamido	methylamino-carbonylmethoxy
	11(13)	2-methylthio-benzyl	H	methane-sulfonamido	propylamino-carbonylmethoxy

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Compound No.	R ¹	R ²	R ³	R ⁴
11(14)	2-methylthio-benzyl	H	methane-sulfonamido	piperazine-carbonylmethoxy
11(15)	2-methylthio-benzyl	H	isopropane-sulfonamide	propoxy
11(16)	2-methylthio-benzyl	H	ethane-sulfonamido	methoxymethoxy
11(17)	2-methylthio-benzyl	H	propane-sulfonamido	methoxymethoxy
11(18)	2-methylthio-benzyl	H	trifluoro-methane-sulfonamido	methoxymethoxy
11(19)	2-methylthio-benzyl	H	methane-sulfonamido	2,2,2-trifluoro-ethoxy

k. International Patent Application Publication No. WO 95/26957

Other compounds for use in the methods provided herein have the formula:



wherein Q is a naphthyl or biphenyl group; A¹, A² and A³ are attached to a phenyl or benzene ring of Q and are independently selected from hydrogen, (1-6C)alkyl, amino(1-6C)alkyl, hydroxy(1-6C)alkyl, N-(1-4C)alkyl]amino(1-6C)alkyl, N,N-[di(1-4C)alkyl]amino(1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, halogeno(1-6C)alkyl, (1-6C)alkoxy, dihalogeno(1-6C)alkoxy, trihalogeno(1-6C)alkoxy, (2-6C)alkenyloxy, (1-4C)alkoxy(1-6C)alkyl, (1-4C)alkylthio(1-6C)alkyl, (1-4C)alkylsulphinyl(1-6C)alkyl, (1-4C)alkylsulphonyl(1-6C)alkyl, (1-4C)alkylenedioxy, (3-6C)cycloalkyl, (3-8C)cycloalkyl(1-6C)alkyl, phenyl, phenyl(1-6C)alkyl, phenoxy, phenyl(1-6C)alkoxy, halogeno, hydroxy, mercapto, cyano, nitro, carboxy, (1-6C)alkoxycarbonyl, (2-6C)alkenyloxycarbonyl, phenyloxycarbonyl, phenyl(1-6C)alkoxycarbonyl, (1-6C)alkanoyl, benzoyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, (1-6C)alkanoylamino, trifluoroacetyl,

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- trifluoroacetamido, N-[(1-4C)alkyl]trifluoroacetamido, benzamido, N-[(1-4C)alkyl]benzamido, carbamoyl, (1-4C)alkylcarbamoyl, di-(1-4C)alkylcarbamoyl, phenylcarbamoyl, sulphamoyl, N-(1-4C)alkylsulphamoyl, N,N-di(1-4C)alkylsulphamoyl, N-phenylsulphamoyl, (1-6C)alkanesulphonamido, benzenesulphonamido, ureido, 3-(1-6C)alkylureido, 3-phenylureido, thioureido, 3-(1-6C)alkylthioureido, 3-phenylthioureido and a group -NRaRb in which Ra and Rb are independently selected from hydrogen, (1-6C)alkyl, phenyl(1-4C)alkyl and (1-6C)alkyl bearing a carboxy or (1-4C)alkoxycarbonyl group, or the group -NRaRb taken together complete a 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 1-piperidinyl or 2-oxo-1-piperidinyl ring; W, X, Y and Z are independently selected from nitrogen and CR² such that two or three of W, X, Y and Z are nitrogen and the remainder are CR², or X is nitrogen and W, Y and Z are CR²; R² has any of the values defined above for A¹, A² or A³; R¹ is selected from (1-6C)alkyl, amino(1-6C)alkyl, hydroxy(1-6C)alkyl, N-[(1-4C)alkyl]amino(1-6C)alkyl, N,N-[di(1-4C)alkyl]amino(1-6C)alkyl, (2-6C)alkenyl, 2-[(1-6C)alkoxycarbonyl]ethenyl, 2-phenylethenyl, (2-6C)alkynyl, (1-6C)alkoxycarbonylethynyl, phenylethynyl, halogeno(1-6C)alkyl, (1-3C)alkoxy, dihalogeno(1-3C)alkoxy, trihalogeno(1-3C)alkoxy, (2-6C)alkenyloxy, (1-4C)alkoxy(1-6C)alkyl, (1-4C)alkylthio(1-6C)alkyl, (1-4C)alkylsulphinyl(1-6C)alkyl, (1-4C)alkylsulphonyl(1-6C)alkyl, (3-6C)cycloalkyl, (3-8C)cycloalkyl(1-6C)alkyl, phenyl(1-6C)alkyl, phenyl(1-3C)alkoxy, halogeno, hydroxy, mercapto, nitro, carboxy, (1-6C)alkoxycarbonyl, (2-6C) alkenyloxy carbonyl, phenyloxy carbonyl, phenyl(1-6C)alkoxycarbonyl, (1-6C)alkanoyl, benzoyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, (1-6C)alkanoylamino, trifluoroacetyl, trifluoroacetamido, N-[(1-4C)alkyl]trifluoroacetamido, benzamido, N-[(1-4C)alkyl]benzamido, carbamoyl, (1-4C)alkylcarbamoyl, di-(1-4C)alkylcarbamoyl, phenylcarbamoyl, sulphamoyl, N-(1-4C)alkylsulphamoyl, N,N-di(1-4C)alkylsulphamoyl, N-phenylsulphamoyl, (1-6C)alkanesulphonamido, benzenesulphonamido, ureido, 3-(1-6C)alkylureido, 3-phenylureido, thioureido, 3-(1-6C)alkylthioureido, 3-phenylthioureido and a group -NRaRb in which Ra and Rb are independently selected from hydrogen, (1-6C)alkyl, (1-4C)alkyl bearing a carboxy or (1-4C)alkoxycarbonyl group, or the group -NRaRb taken together complete a 1-pyrrolidinyl, 2-oxo-pyrrolidinyl, 1-piperidinyl or 2-oxo-1-piperidinyl ring; or when X or Y is CR², R¹ together with the adjacent R² is (3-5C)alkylene or (3-5C)alkenylene which together with the carbon atoms to which R¹ and the adjacent R² are attached complete a 5-7 membered ring; and wherein any of said phenyl, naphthyl

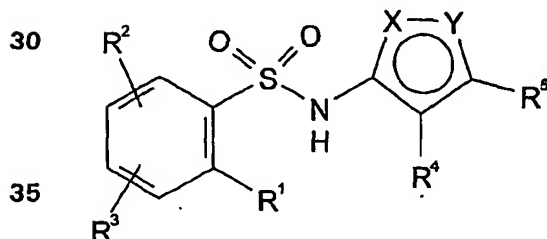
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or benzene moieties of A¹, A², A³, R¹ or R² may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or a pharmaceutically-acceptable salt thereof.

- Preferred compounds of this embodiment include 5-dimethylamino-N-(3-methoxy-5-methyl-2-pyrazinyl)-1-naphthalenesulphonamide; 5-dimethylamino-N-(5-chloro-3-methoxy-2-pyrazinyl)-1-naphthalenesulphonamide; 5-dimethylamino-N-(5-bromo-3-methoxy-2-pyrazinyl)-1-naphthalenesulphonamide; 5-ethylamino-N-(5-bromo-3-methoxy-2-pyrazinyl)-1-naphthalenesulphonamide; 5-ethylamino-N-(6-chloro-3-pyridazinyl)-1-naphthalenesulphonamide; 5-ethylamino-N-(5-bromo-2-pyrazinyl)-1-naphthalenesulphonamide; 5-dimethylamino-N-(2-chloro-4-methoxy-5-pyrimidinyl)-1-naphthalenesulphonamide; N-(5-bromo-3-methoxy-2-pyrazinyl)-4'-isobutyl-2-biphenylsulphonamide; N-(5-bromo-3-methoxy-2-pyrazinyl)-4'-methyl-2-biphenylsulphonamide; N-(5-bromo-3-methoxy-2-pyrazinyl)-2-biphenylsulphonamide; N-(5-chloro-3-methoxy-2-pyrazinyl)-2-biphenylsulphonamide; N-(3-methoxy-5-methyl-2-pyrazinyl)-2-biphenylsulphonamide; N-(2-chloro-4-methoxy-5-pyrimidinyl)-2-biphenylsulphonamide; 5-dimethylamino-N-(5-ethynyl-3-methoxy-2-pyrazinyl)-1-naphthalenesulphonamide; N-(5-bromo-3-methoxy-2-pyrazinyl)-5-(isopropylamino)-1-naphthalenesulphonamide; 4'-isobutyl-N-(3-methoxy-5-methyl-2-pyrazinyl)-2-biphenylsulphonamide; N-(5-chloro-3-methoxy-2-pyrazinyl)-4'-isobutyl-2-biphenylsulphonamide; N-(5-bromo-3-methoxy-2-pyrazinyl)-4'-methoxy-2-biphenylsulphonamide; 4'-methoxy-N-(3-methoxy-5-methyl-2-pyrazinyl)-2-biphenylsulphonamide; N-(3-methoxy-5-methyl-2-pyrazinyl)-4'-methyl-2-biphenylsulphonamide; 4'-chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-2-biphenylsulphonamide; 4'-isobutyl-N-(3-methoxy-5-methyl-2-pyrazinyl)-3'-nitro-2-biphenylsulphonamide; and 3'-amino-4'-isobutyl-N-(3-methoxy-5-methyl-2-pyrazinyl)-2-biphenylsulphonamide; or a pharmaceutically acceptable salt thereof.

I. European Patent Application Publication No. EP 0569 193 A1

Also of interest herein for use in the methods are compounds of the formula:



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- and pharmaceutically acceptable salts thereof, where one of X and Y is N and the other is O; R¹, R² and R³ are each independently (a) hydrogen, except that R¹ is other than hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, or aralkoxy, any of which may be substituted
- 5 with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) -C(O)H or -C(O)R⁶; (h) -CO₂H or CO₂R⁶; (i) -SH, -S(O)_nR⁶, -S(O)_m-OH, -S(O)_m-OR⁶, -O-S(O)_m-R⁶, -O-S(O)_mOH, or -O-S(O)_m-OR⁶; (j) -Z⁴-NR⁷R⁸; or (k) -Z⁴-N(R¹¹)-Z⁵-NR⁹R¹⁰; R⁴ and R⁵ are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, or aralkoxy, any of which may be substituted
- 10 with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) -C(O)H or -C(O)R⁶; (h) -CO₂H or CO₂R⁶; (i) -SH, -S(O)_nR⁶, -S(O)_m-OH, -S(O)_m-OR⁶, -O-S(O)_m-R⁶, -O-S(O)_mOH, or -OS(O)_m-OR⁶; (j) -Z⁴-NR⁷R⁸; or (k) -Z⁴-N(R¹¹)-Z⁵-NR⁹R¹⁰; (l) R⁴ and R⁵ together are alkylene or alkenylene (either of which may be substituted with Z¹, Z² and Z³), completing a 4- to 8- membered saturated, unsaturated or aromatic ring together with the carbon atoms to
- 15 which they are attached; R⁶ is alkyl, alkenyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; R⁷ is (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; (c) cyano; (d) hydroxyl; (e) -C(O)H or -C(O)R⁶; (f) -CO₂R⁶;
- 20 (g) -SH, -S(O)_nR⁶, -S(O)_m-OH, -S(O)_m-OR⁶, -O-S(O)_m-R⁶, -O-S(O)_mOH, or -O-S(O)_m-OR⁶, except when Z⁴ is -S(O)_n; R⁸ is (a) hydrogen; (b) -C(O)H or -C(O)R⁶, except when Z⁴ is -C(O)- and R⁷ is -C(O)H, -C(O)R⁶, or -CO₂R⁶; (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; or R⁷ and R⁸ together are alkylene or alkenylene (either of
- 25 which may be substituted with Z¹, Z² and Z³), completing a 3- to 8- membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached; R⁹ is (a) hydrogen; (b) hydroxyl; (c) -C(O)H or -C(O)R⁶; (d) -CO₂R⁶; (e) -SH, -S(O)_nR⁶, -S(O)_m-OH, -S(O)_m-OR⁶, -O-S(O)_m-R⁶, -O-S(O)_mOH, or -O-S(O)_m-OR⁶; (f) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³;
- 30 R¹⁰ is (a) hydrogen; (b) -C(O)H or -C(O)R⁶, except when Z⁵ is -C(O)- and R⁹ is -C(O)H, -C(O)R⁶, or -CO₂R⁶; or (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; R¹¹ is (a) hydrogen; (b) hydroxyl; (c) -C(O)H, -C(O)R⁶ or CO₂R⁶; or (d)

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- alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; or any two of R^9 , R^{10} and R^{11} together are alkylene or alkenylene (either of which may be substituted with Z^1 , Z^2 and Z^3), completing a 3- to 8- membered saturated, unsaturated or aromatic ring
- 5 together with the atoms to which they are attached; Z^1 , Z^2 and Z^3 are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkyl; (e) alkenyl; (f) aralkyl; (g) alkoxy; (h) aryloxy; (i) aralkoxy; (j) -SH, -S(O)_nZ⁶, -S(O)_m-OH, -S(O)_m-OZ⁶, -O-S(O)_m-Z⁶, -O-S(O)_mOH, or -O-S(O)_m-O-Z⁶; (k) oxo; (l) nitro; (m) cyano; (n) -C(O)H or -C(O)Z⁶; (o) -CO₂H or -CO₂Z⁶; (p) -Z⁴-NZ⁷Z⁸; (q) Z⁴-N(Z¹¹)-Z⁵-Z⁶; or (r) -Z⁴-N(Z¹¹)-Z⁵-NZ⁷Z⁸; Z⁴ and Z⁵
- 10 are each independently (a) a single bond; (b) -Z⁹-S(O)_n-Z¹⁰-; (c) -Z⁹-C(O)-Z¹⁰-; (d) -Z⁹-C(S)-Z¹⁰-; (e) -Z⁹-O-Z¹⁰-; (f) -Z⁹-S-Z¹⁰-; or (g) -Z⁹-O-C(O)-Z¹⁰-; Z⁶, Z⁷ and Z⁸ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, or Z⁷ and Z⁸ together are alkylene or alkenylene, completing a 3- to 8- membered saturated, unsaturated or aromatic ring together with
- 15 the nitrogen atom to which they are attached; Z⁹ and Z¹⁰ are each independently a single bond, alkylene, alkenylene, or alkynylene; Z¹¹ is (a) hydrogen; (b) hydroxyl; (c) -C(O)H, -C(O)Z⁶ or -CO₂Z⁶; (d) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl; or any two of Z⁷, Z⁸ and Z¹¹ together are alkylene or alkenylene, completing a 3- to 8- membered saturated, unsaturated, or
- 20 aromatic ring together with the atoms to which they are attached; m is 1 or 2; and n is 0, 1, or 2.

For this embodiment, it is preferred that R¹ is phenyl or phenoxy, optionally substituted with alkyl, alkoxy, -NZ⁷Z⁸, halo, or hydroxy; R² and R³ are each independently hydrogen, alkyl, or -NR⁷R⁸; R⁴ and R⁵ are alkyl; and R⁷, R⁸, Z⁷ and Z⁸ are

25 each independently hydrogen, alkyl, or -C(O)alkyl.

For this embodiment, most preferred compounds are those wherein R¹ is phenyl or phenoxy, optionally substituted with alkyl, alkoxy, amino, alkylamino, dialkylamino, alkanoylamino or hydroxy; R² and R³ are each independently hydrogen, alkyl of 1 to 4 carbon atoms, amino, alkylamino, dialkylamino, or alkanoylamino; and R⁴ and R⁵ are

30 alkyl of 1 to 4 carbon atoms, specially methyl.

Preferred compounds of this embodiment include N-3,4-Dimethyl-5-isoxazolyl)[1, 1'-biphenyl]-2-sulfonamide; N-3,4-Dimethyl-5-isoxazolyl)-2-bromobenzene-sulfonamide; N-3,4-Dimethyl-5-isoxazolyl)-2-phenoxybenzene-sulfonamide; 3'-Amino-N-(3,4-dimethyl-5-isoxazolyl)[1, 1'-biphenyl]-2-sulfonamide; 2-Fluoro-N-(3,4-dimethyl-

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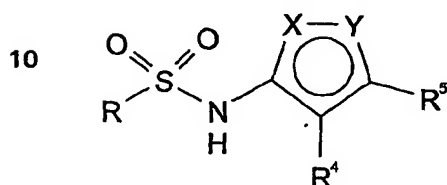
- 5isoxazoly)benzene-sulfonamide; N-[3-[(3,4-Dimethyl-5-isoxazoly)-2-methyl-benzenesulfonamide; 5-Amino-N-(3,4-Dimethyl-5isoxazoly)-2-methyl-benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-2-(1-methylethyl)-benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-2-nitro-benzenesulfonamide; 2-
- 5 Amino-N-(3,4-dimethyl-5-isoxazoly)benzene-sulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-4'-methyl[1,1'-biphenyl]-2-sulfonamide; 2'-Amino-N-(3,4-dimethyl-5-isoxazoly)-[1,1'-biphenyl]-2-sulfonamide; 3'-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazoly)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-2-(trifluoromethyl)-benzenesulfonamide; 2-Chloro-N-(3,4-dimethyl-5-isoxazoly)-6-methylbenzene-
- 10 sulfonamide; 4'-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazoly)[1,1'-biphenyl]-2-sulfonamide; N-[2'-[[[(3,4-Dimethyl-5-isoxazoly)amino]sulfonyl][1,1-biphenyl]-3-y]acetamide; N-(3,4-Dimethyl-5-isoxazoly)-4'-propyl[1,1'-biphenyl]-2-sulfonamide; 2-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazoly)benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-4'-(2-methylpropyl)-[1,1'-biphenyl]-2-sulfonamide; 4'-Butyl-N-(3,4-dimethyl-5-
- 15 isoxazoly)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-dimethyl-5-isoxazoly)-2-(1-naphthalenyl)-benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-3'-(2-methylpropyl)-[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-4'-(2-methylpropoxy)-[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-4'-(1-methylethoxy)-[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-4'-(phenylmethoxy)-[1,1'-
- 20 biphenyl]-2-sulfonamide; 4'-(1,1-Dimethylethyl)-N-(3,4-dimethyl-5-isoxazoly)-[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-4'-methoxy-[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazoly)-4'-[(1-methylethyl)-amino][1,1'-biphenyl]-2-sulfonamide; 2-[[[2'-[[[(3,4-Dimethyl-5-isoxazoly)amino]sulfonyl]-[1,1'-biphenyl]-4-yl](1-methylethyl)amino]carbonyl]-amino]-4-methylpentanoic acid, ethyl ester; 2'-Amino-N-
- 25 (3,4-dimethyl-5-isoxazoly)-4'-(2-methyl-propyl)[1,1'-biphenyl]-2-sulfonamide; N-[2'-[[[(3,4-Dimethyl-5-isoxazoly)amino]sulfonyl][1,1'-biphenyl]-4-yl]]-N-(1-methylethyl)- β -phenylbenzenepropanamide; 2'-Nitro-N-(3,4-dimethyl-5-isoxazoly)-[1,1'-biphenyl]-2-sulfonamide; 5-[[[(2-phenyl)phenyl]sulfonyl]amino]-3-methyl-4-isoxazolecarboxylic acid, ethyl ester; N-(3-Methyl-4-phenylmethyl-5-isoxazoly)-4'-(2-methylpropyl)-[1,1'-
- 30 biphenyl]-2-sulfonamide; N-(4,5-Dimethyl-3-isoxazoly)-4'-(2-methylpropyl)-[1,1'-biphenyl]-2-sulfonamide; 4'-(2-Methylpropyl)-2'-Methoxy-N-(3,4-dimethyl-5-isoxazoly)-[1,1'-biphenyl]-2-sulfonamide; 4'-(2-Methylpropyl)-2'-hydroxy-N-(3,4-dimethyl-5-isoxazoly)-[1,1'-biphenyl]-2-sulfonamide; N-(3-Methyl-4-nitro-5-isoxazoly)-4'-(2-methylpropyl)-[1,1'-biphenyl]-2-sulfonamide; N-(4-Methyl-5-isoxazoly)-4'-(2-

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- methylpropyl)-[1,1'-biphenyl]-2-sulfonamide; 4'-(2-Methylpropyl)-N-(4,5,6,7-tetrahydro-2,1-benzisoxazol-3-yl)-[1,1'-biphenyl]-2-sulfonamide; 4-Amino-4'-(2-methylpropyl)-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide; 2'-Fluoro-4'-(2-methylpropyl)-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide; or 4-Methoxy-4'-(2-methylpropyl)-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide.

m. European Patent Application Publication No. EP 0 556 258 A1

Compounds of the formula:



- and pharmaceutically or veterinarily acceptable salts thereof are also intended for use in the methods provided herein. The above symbols are defined as follows: one of X and Y is N and the other is O; R is naphthyl or naphthyl substituted with R¹, R² and R³; R¹, R² and R³ are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) -C(O)H or -C(O)R⁶; (h) -CO₂H or -CO₂R⁴; (i) -SH, -S(O)_RR⁴, -S(O)_m-OH, -S(O)_m-OR⁴, -O-S(O)_m-R⁴, -O-S(O)_mOH, or -O-S(O)_m-OR⁴; (j) -Z⁴-NR⁷R⁸; or (k) -Z⁴-N(R¹¹)-Z⁶-NR⁹R¹⁰; R⁴ and R⁵ are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) -C(O)H or -C(O)R⁴; (h) -CO₂H or -CO₂R⁴; (i) -SH, -S(O)_RR⁴, -S(O)_m-OH, -S(O)_m-OR⁴, -O-S(O)_m-R⁴, -O-S(O)_mOH, or -O-S(O)_m-OR⁴; (j) -Z⁴-NR⁷R⁸; (k) -Z⁴-N(R¹¹)-Z⁶-NR⁹R¹⁰; or (l) R⁴ and R⁵ together are alkylene or alkenylene (either of which may be substituted with Z¹, Z² and Z³), completing a 4- to 8-membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached; R⁴ is alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; R⁷ is (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; (c) cyano; (d) hydroxyl; (e) -C(O)H or -C(O)R⁴; (f) -CO₂H or -CO₂R⁴; (g) -SH, -S(O)_RR⁸, -S(O)_m-OH, -S(O)_m-OR⁶, -O-S(O)_m-R⁶, -O-S(O)_mOH, or -O-S(O)_m-OR⁶, except when Z⁶ is -S(O)_R-; R⁸ is (a) hydrogen; (b) -C(O)H or

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- C(O)R⁶, except when Z⁴ is -C(O)- and R⁷ is -C(O)- and R⁷ is -C(O)H, -C(O)R⁶, -CO₂H, or -CO₂R⁶; (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; or R⁷ and R⁶ together are alkylene or alkenylene (either of which may be substituted with Z¹, Z² and Z³), completing 3- to 8-membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached; R⁶ is (a) hydrogen; (b) hydroxyl; (c) -C(O)H or -C(O)R⁶; (d) -CO₂H or -CO₂R⁶; (e) -SH, -S(O)_nR⁴, -S(O)_m-OH, -S(O)_m-OR⁶, -O-S(O)_m-R⁶, -O-S(O)_m-R⁶, -O-S(O)_m-R⁶, -O-S(O)_mOH, or -O-S(O)_m-OR⁶; (f) alkyl, alkynyl, alkenyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; R¹⁰ is (a) hydrogen; (b) -C(O)H or -C(O)R⁶, except when Z⁶ is -C(O)- and R⁹ is -C(O)R⁶, -CO₂H, or -CO₂R⁶; (c) alkyl, alkenyl, alkenyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; R¹¹ is (a) hydrogen; (b) hydroxyl, CO₂R⁶ or CO₂H, except when one of R⁹ and R¹⁰ is hydroxyl, CO₂R⁶ or CO₂H; (c) -C(O)H or -C(O)R⁶; or (d) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; or any two of R⁹, R¹⁰ and R¹¹ together are alkylene or alkenylene (either of which may be substituted with Z¹, Z² and Z³), completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the atoms to which they are attached; Z¹, Z² and Z³ are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkoxy; (e) -SH, -S(O)_nZ⁶, -S(O)_m-OH, -S(O)_m-OZ⁶, -O-S(O)_m-Z⁶, -O-S(O)_mOH, or -O-S(O)_m-OZ⁶; (f) oxo; (g) nitro; (h) cyano; (i) -C(O)H or -C(O)Z⁶; (j) -CO₂H or CO₂Z⁶; or (k) -NZ⁷Z⁶, -C(O)NZ⁷Z⁶, or -S(O)RZ⁷Z⁶; Z⁴ and Z⁵ are each independently (a) a single bond; (b) -S(O)_n-; (c) -C(O)-; (d) -C(S)-; or (e) alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z¹, Z² and Z³; Z⁶, Z⁷, and Z⁸ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, or Z⁷ and Z⁸ together are alkylene or alkenylene, completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached; m is 1 or 2; and n is 0, 1, or 2.

Preferred compounds of this embodiment include 5-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; N-[5-[(3,4-Dimethyl-5-isoxazolyl)amino]-sulfonyl]-1-naphthalenyl]acetamide; 5-Amino-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; N-[6-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenyl]acetamide;

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- 5-Amino-N-(3,4-dimethyl-5-isoxazolyl)-2-naphthalenesulfonamide; N-[4-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenyl]acetamide; N-[6-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-naphthalenyl]acetamide; 6-Amino-N-(3,4-dimethyl-5-isoxazolyl)-2-naphthalenesulfonamide; 4-Amino-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; 5-Dimethylamino-N-(4,5-dimethyl-3-isoxazolyl)-1-naphthalenesulfonamide; N-[5-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-1-naphthalenyl]acetamide; N-[5-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-2-naphthalenyl]acetamide; N-[8-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-2-naphthalenyl]acetamide; N-[7-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-2-naphthalenyl]acetamide; N-[7-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenyl]acetamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-methoxy-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; 5-[(1-Methylethyl)amino]-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; N-[5-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenyl]-2-methylpropanamide; 5-Chloro-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-[(phenylmethyl)amino]-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-hydroxy-1-naphthalenesulfonamide; 7-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-[methyl(1-methylethyl)amino]-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(2-oxo-1-pyrrolidiny)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(2-oxo-1-piperidiny)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-[(phenylamino)thioxomethyl]amino]-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(1-pyrrolidiny)-1-naphthalenesulfonamide; 5-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenecarboxylic acid; 5-[[[(5-(Dimethylamino)-1-naphthalenyl)sulfonyl]amino]-3-methyl-4-isoxazolecarboxylic acid, ethyl ester; 5-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenecarboxylic acid, methyl ester; 5-(Dimethylamino)-N-(3-methyl-5-isoxazolyl)-1-naphthalenesulfonamide; 5-[(Dimethylamino)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide, trifluoroacetate (1:1) salt; N-(3,4-Dimethyl-5-isoxazolyl)-5-(1-hydroxy-1-methylethyl)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(1-methylethenyl)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(1-piperidiny)-1-naphthalenesulfonamide; trifluoroacetate (2:1) salt; N-(3,4-Dimethyl-5-isoxazolyl)-5-(methylamino)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(ethylamino)-1-naphthalenesulfonamide; N-(3-Methyl-4-phenylmethyl-5-isoxazolyl)-5-[dimethylamino]-1-naphthalenesulfonamide; N-(3-Methyl-4-phenyl-5-isoxazolyl)-5-(dimethylamino)-1-naphthalenesulfonamide; N-(3-Ethyl-4-methyl-5-isoxazolyl)-5-

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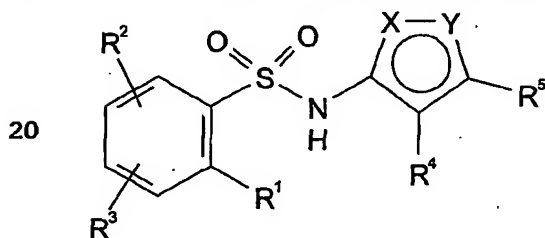
- 5-Amino-N-(3,4-dimethyl-5-isoxazolyl)-2-naphthalenesulfonamide; N-[4-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenyl]acetamide; N-[6-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-naphthalenyl]acetamide; 6-Amino-N-(3,4-dimethyl-5-isoxazolyl)-2-naphthalenesulfonamide; 4-Amino-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; 5-Dimethylamino-N-(4,5-dimethyl-3-isoxazolyl)-1-naphthalenesulfonamide; N-[5-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-1-naphthalenyl]acetamide; N-[5-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-2-naphthalenyl]acetamide; N-[8-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-2-naphthalenyl]acetamide; N-[7-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-2-naphthalenyl]acetamide; N-[7-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenyl]acetamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-methoxy-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; 5-[(1-Methylethyl)amino]-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; N-[5-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenyl]-2-methylpropanamide; 5-Chloro-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-[(phenylmethyl)amino]-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-hydroxy-1-naphthalenesulfonamide; 7-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-[methyl(1-methylethyl)amino]-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(2-oxo-1-pyrrolidinyl)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(2-oxo-1-piperidinyl)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-[(phenylamino)thioxomethyl]amino]-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(1-pyrrolidinyl)-1-naphthalenesulfonamide; 5-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenecarboxylic acid; 5-[[5-(Dimethylamino)-1-naphthalenyl]sulfonyl]amino]-3-methyl-4-isoxazolecarboxylic acid, ethyl ester; 5-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-1-naphthalenecarboxylic acid, methyl ester; 5-(Dimethylamino)-N-(3-methyl-5-isoxazolyl)-1-naphthalenesulfonamide; 5-[(Dimethylamino)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide, trifluoroacetate (1:1) salt; N-(3,4-Dimethyl-5-isoxazolyl)-5-(1-hydroxy-1-methylethyl)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(1-methylethenyl)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(1-piperidinyl)-1-naphthalenesulfonamide, trifluoroacetate (2:1) salt; N-(3,4-Dimethyl-5-isoxazolyl)-5-(methylamino)-1-naphthalenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-5-(ethylamino)-1-naphthalenesulfonamide; N-(3-Methyl-4-phenylmethyl-5-isoxazolyl)-5-[dimethylamino]-1-naphthalenesulfonamide; N-(3-Methyl-4-phenyl-5-isoxazolyl)-5-(dimethylamino)-1-naphthalenesulfonamide; N-(3-Ethyl-4-methyl-5-isoxazolyl)-5-

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(dimethylamino)-1-naphthalenesulfonamide; 5-(Dibutylamino)-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide, monosodium salt; 4-[1-[(3,4-Dimethyl-5-isoxazolyl)-amino]sulfonyl]naphthalen-5-yl]amino]butanoic acid; 6-Amino-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; 7-Amino-N-(3,4-dimethyl-5-isoxazolyl)-2-naphthalenesulfonamide; 8-Amino-N-(3,4-dimethyl-5-isoxazolyl)-2-naphthalenesulfonamide; 7-Amino-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; 7-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)-2-naphthalenesulfonamide; 8-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)-2-naphthalenesulfonamide; 6-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide; 5-(Dimethylamino)-N-(3-methyl-4-nitro-5-isoxazolyl)-1-naphthalenesulfonamide; 5-(Dimethylamino)-N-(4,5,6,7-tetrahydro-2,1-benisoaxazol-3-yl)-1-naphthalenesulfonamide; 5-(Dimethylamino)-N-(4-ethyl-3-methyl-5-isoxazolyl)-1-naphthalenesulfonamide; or 5-(Dimethylamino)-N-(4-methyl-5-isoxazolyl)-1-naphthalenesulfonamide.

n. U.S. Patent No. 5,514,696

For use in the methods provided herein are compounds of the formula:



and pharmaceutically acceptable salts thereof, where one of X and Y is N and the other is O; R¹, R² and R³ are each independently (a) hydrogen, except that R¹ is other than hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) -C(O)H or -C(O)R⁶; (h) -CO₂ H or -CO₂ R⁶; (i) -SH, -S(O)ₙ R⁶, -S(O)ₘ -OH, -S(O)ₘ -OR⁶, -O-S(O)ₘ -R⁶, -O-S(O)ₘ OH or -O-S(O)ₘ -OR⁶; (j) -Z⁴ -NR⁷ R⁸; or (k) -Z⁴ -N(R¹¹)-Z⁵ -NR⁹ R¹⁰; R⁴ and R⁵ are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) -C(O)H or -C(O)R⁶; (h) -CO₂ H or -CO₂ R⁶; (i) -SH, -S(O)ₙ R⁶, -S(O)ₘ -OH, -S(O)ₘ -OR⁶, -O-S(O)ₘ -R⁶, -O-S(O)ₘ OH or -O-S(O)ₘ -OR⁶; (j) -Z⁴ -NR⁷ R⁸; (k) -Z⁴ -N(R¹¹)-Z⁵ -NR⁹ R¹⁰; or (l) R⁴ and R⁵ together are alkylene or

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alkenylene (either of which may be substituted with Z^1 , Z^2 and Z^3), completing a 4- to 8-membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached; R^6 is alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; R^7 is (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; (c) cyano; (d) hydroxyl; (e) $-C(O)H$ or $-C(O)R^6$; (f) $-CO_2 R^6$; (g) $-SH$, $-S(O)R^6$, $-S(O)-OH$, $-S(O)-OR^6$, $-O-S(O)-R^6$, $-O-S(O)OH$ or $-O-S(O)-OR^6$, except when Z^4 is $-S(O)_n-$; R^8 is (a) hydrogen; (b) $-C(O)H$ or $-C(O)R^6$, except when Z^4 is $-C(O)-$ and R^7 is $-C(O)H$, $-C(O)R^6$ or $-CO_2 R^6$; (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; or R^7 and R^8 together are alkylene or alkenylene (either of which may be substituted with Z^1 , Z^2 and Z^3), completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached; R^9 is (a) hydrogen; (b) hydroxyl; (c) $-C(O)H$ or $-C(O)R^6$; (d) $-CO_2 R^6$; (e) $-SH$, $-S(O)_n R^6$, $-S(O)_m -OH$, $-S(O)_m -OR^6$, $-O-S(O)_m -R^6$, $-O-S(O)_m OH$ or $-O-S(O)_m -OR^6$; (f) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; R^{10} is (a) hydrogen; (b) $-C(O)H$ or $-C(O)R^6$, except when Z^5 is $-C(O)-$ and R^9 is $-C(O)H$, $-C(O)R^6$ or $-CO_2 R^6$; or (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; R^{11} is (a) hydrogen; (b) hydroxyl; (c) $-C(O)H$, $-C(O)R^6$ or $CO_2 R^6$; or (d) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; or any two of R^9 , R^{10} and R^{11} together are alkylene or alkenylene (either of which may be substituted with Z^1 , Z^2 and Z^3), completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the atoms to which they are attached; Z^1 , Z^2 and Z^3 are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkyl; (e) alkenyl; (f) aralkyl; (g) alkoxy; (h) aryloxy; (i) aralkoxy; (j) $-SH$, $-S(O)_n Z^6$, $-S(O)_m -OH$, $-S(O)_m -OZ^6$, $-O-S(O)_m -Z^6$, $-O-S(O)_m OH$ or $-O-S(O)_m -OZ^6$; (k) oxo; (l) nitro; (m) cyano; (n) $-C(O)H$ or $-C(O)Z^6$; (o) $-CO_2 H$ or $-CO_2 Z^6$; (p) $-Z^4 -NZ^7 Z^8$; (q) $-Z^4 -N(Z^{11})-Z^5 -Z^6$; or (r) $-Z^4 -N(Z^{11})-Z^5 -NZ^7 Z^8$; Z^4 and Z^5 are each independently (a) a single bond; (b) $-Z^9 -S(O)_n -Z^{10}-$; (c) $-Z^9 -C(O)-Z^{10}$; (d) $-Z^9 -C(S)-Z^{10}-$; (e) $-Z^9 -O-Z^{10}-$; (f) $-Z^9 -S-Z^{10}-$; or (g) $-Z^9$

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$\text{--O--C(O)--Z}^{10}\text{--}$; Z^6 , Z^7 and Z^8 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, or Z^7 and Z^8 together are alkylene or alkenylene, completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are
 5 attached; Z^9 and Z^{10} are each independently a single bond, alkylene, alkenylene or alkynylene; Z^{11} is (a) hydrogen; (b) hydroxyl; (c) --C(O)H , --C(O)Z^6 or $\text{--CO}_2\text{Z}^6$; (d) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl; or any two of Z^7 , Z^8 and Z^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the atoms to
 10 which they are attached; m is 1 or 2; and n is 0, 1 or 2.

For this embodiment, it is preferred that R^1 is phenyl or phenoxy, optionally substituted with one or more alkyl, alkoxy, $\text{--NZ}^7\text{Z}^8$, halo and hydroxy; R^2 and R^3 are each independently hydrogen, alkyl or $\text{--NR}^7\text{R}^8$; R^4 and R^5 are alkyl; and R^7 , R^8 , Z^7 and Z^8 are each independently hydrogen, alkyl or --C(O)alkyl .

15 In preferred embodiments, R^1 is phenyl or phenoxy, optionally substituted with alkyl, alkoxy, amino, alkylamino, dialkylamino, alkanoylamino or hydroxy; R^2 and R^3 are each independently hydrogen, alkyl of 1 to 4 carbon atoms, amino, alkylamino, dialkylamino or alkanoylamino; and R^4 and R^5 are alkyl of 1 to 4 carbon atoms, especially methyl.

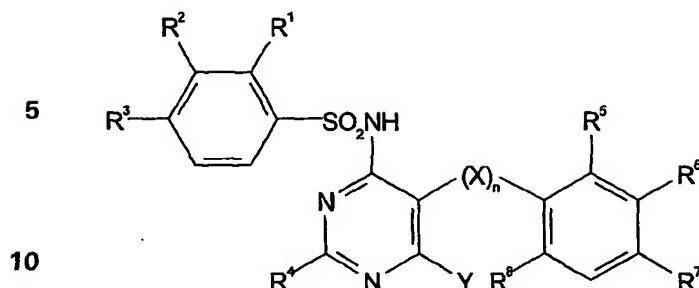
20 Preferred compounds of this embodiment include N-(3,4-Dimethyl-5-isoxazolyl)-2-bromobenzene-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-phenoxybenzene-sulfonamide; 2-Fluoro-N-(3,4-dimethyl-5-isoxazolyl)benzene-sulfonamide; N-[3-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-4-methylphenyl]acetamide; 5-Amino-N-(3,4-Dimethyl-5-isoxazolyl)-2-methyl-benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-(1-
 25 methylethyl)benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-nitro-benzenesulfonamide; 2-Amino-N-(3,4-dimethyl-5-isoxazolyl)benzene-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-(trifluoromethyl)-benzenesulfonamide; 2-Chloro-N-(3,4-dimethyl-5-isoxazolyl)-6-methylbenzene-sulfonamide; 2-(Dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide; and N-(3,4-Dimethyl-5-isoxazolyl)-2-(1-naphthalenyl)-
 30 benzenesulfonamide.

o. U.S. Patent No. 5,420,129

In particular, the compounds for use in the methods provided herein are of the formula:

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- wherein R¹ is hydrogen, lower-alkyl, lower-alkoxy, lower-alkylthio, halogen or trifluoromethyl; R² is hydrogen, lower-alkyl, halogen, lower-alkoxy, trifluoromethyl or -OCH₂ COOR⁹; R³ is hydrogen, lower-alkyl, halogen, lower-alkylthio, trifluoromethyl, lower-alkoxy or trifluoromethoxy; R² and R³ together are butadienyl, methylenedioxy, ethylene-dioxy or isopropylidenedioxy; R⁴ is hydrogen, lower-alkyl, trifluoromethyl, lower-alkoxy, lower-alkylthio, hydroxy-lower-alkyl, hydroxy-lower-alkoxy, hydroxy-lower-alkoxy-lower-alkyl, hydroxy-lower-alkoxy-lower-alkoxy, alkoxy-lower-alkyl, alkoxy-lower-alkyloxy, lower-alkylsulfinyl, lower-alkylsulfonyl, 2-methoxy-3-hydroxypropoxy, 2-hydroxy-3-phenylpropyl, amino-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, amino, lower-alkylamino, di-lower-alkylamino, arylamino, aryl, arylthio, aryloxy, aryl-lower-alkyl, heterocyclyl, heterocyclyl-lower-alkyl, heterocyclylamino, heterocyclylthio, heterocyclylloxy, -CHO, -CH₂ OH or -CH₂Cl; R⁵ to R⁸ are independently hydrogen, halogen, trifluoromethyl, lower-alkoxy, lower-alkylthio or cyano; R⁶ and R⁵ or R⁷ together are butadienyl, methylene-dioxy, ethylenedioxy or isopropylidenedioxy; X is -O- or -S-; Y is -CHO, C₁₋₄-alkyl, -(CH₂)₁₋₄-Z-R₉, -(CH₂)₁₋₄-OC(O)(CH₂)₁₋₄CH₃, -(CH₂)₁₋₄OC(O)Het, -(CH₂)₁₋₄NHC(O)R¹⁰, -(CH₂)₁₋₄OCH₂CH(OH)CH₂OH and cyclic ketals thereof, -(CH₂)₁₋₄NR⁹CH₂CH(OH)CH₂OH, -(CH₂)₁₋₄OCH₂CH₂SCH₃, -(CH₂)₁₋₄OCH₂CH₂S(O)CH₃, -(CH₂)₁₋₄O(CH₂)₁₋₄-Z H, -(CH₂)₁₋₄O(CH₂)₁₋₄OC(O)R¹⁰, -(CH₂)₁₋₄NR⁹(CH₂)₁₋₄Z H, -(CH₂)₁₋₄O(CH₂)₁₋₄OC(O)Het, -(CH₂)₀₋₃CH(OH)R¹⁰, -(CH₂)₀₋₃CH(OH)(CH₂)₁₋₄Z H, -(CH₂)₀₋₃CH(OH)CH₂SCH₃, -(CH₂)₀₋₃CH(OH)CH₂S(O)CH₃, -(CH₂)₀₋₃CH(OH)OCH₂CH₂OH, -(CH₂)₀₋₃C(O)(CH₂)₁₋₄CH₃, -(CH₂)₀₋₃C(O)(CH₂)₁₋₄Z R¹¹, -(CH₂)₀₋₃C(O)CH₂Hal, -(CH₂)₁₋₄Hal, -(CH₂)₁₋₄CN, -(CH₂)₀₋₃C(O)OR⁹, -OR¹² or -SR¹²; R⁹ is hydrogen or C₁₋₄-alkyl; R¹⁰ is C₁₋₄-alkyl; R¹¹ is hydrogen, C₁₋₄-alkanoyl or heterocyclylcarbonyl; R¹² is C₁₋₄-alkyl or -(CH₂)₀₋₄-aryl; Z is -O-, -S- or -NR⁹-; Het is a heterocyclic residue; Hal is halogen; and n is 0 or 1; and salts thereof.

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- Preferred compounds of this embodiment include 4-tert-butyl-N-[6-ethoxy-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl]benzenesulphonamide, 4-tert-butyl-N-[6-methoxy-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl]benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-methyl-2-(morpholin-4-yl)-pyrimidin-4-yl]-
- 5 benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-formyl-2-(morpholin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-hydroxymethyl-2-(morpholin-4-yl)-pyrimidin-4-yl]benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-chloromethyl-2-(morpholin-4-yl)-pyrimidin-4-yl]benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-
- 10 6-(2-hydroxy-ethoxymethyl)-2-(morpholin-4-yl)-pyrimidin-4-yl]benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-methyl-pyrimidin-4-yl]-benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-formyl-pyrimidin-4-yl]-benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-hydroxymethyl-pyrimidin-4-yl]-benzenesulphonamide, 4-tert-butyl-N-[6-chloromethyl-5-(2-chloro-
- 15 5-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy-methyl)-pyrimidin-4-yl]-benzenesulphonamide, thiophene-3-carboxylic acid 2-[6-(4-tert-butylphenylsulphonamino)-5-(2-chloro-5-methoxy-phenoxy)-2-(morpholin-4-yl)-pyrimidin-4-yl-methoxy]ethyl ester, (R,S)-4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy-
- 20 methyl)-2-morpholin-4-yl]-pyrimidin-4-yl]-benzenesulphonamide, (R,S)-4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2,3-dihydroxy-propoxymethyl)-2-(morpholin-4-yl)-pyrimidin-4-yl]benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethylaminomethyl)-pyrimidin-4-yl]-benzenesulphonamide, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(3-hydroxy-propoxymethyl)-pyrimidin-4-yl]-benzene-
- 25 sulphonamide, (RS)-4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2,3-dihydroxy-propylaminomethyl)-pyrimidin-4-yl]-benzenesulphonamide, (RS)-4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxymethyl)-pyrimidin-4-yl]benzenesulphonamide, (RS)-4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2,3-dihydroxy-propoxymethyl)-pyrimidin-4-yl]-benzenesulphonamide, pyridin-3-ylacetic acid
- 30 2-[6-(4-tert-butyl-phenylsulphonyl-amino)-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-ylmethoxy]ethyl ester, pyridin-4-ylacetic acid 2-[6-(4-tert-butyl-phenylsulphonyl-amino)-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-ylmethoxy]ethyl ester, furan-3-carboxylic acid 2-[6-(4-tert-butyl-phenylsulphonyl-amino)-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-ylmethoxy]ethyl ester, thiophene-3-carboxylic acid 2-[6-(4-tert-butyl-

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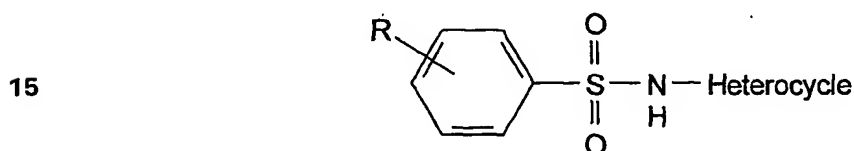
- phenylsulphonyl-amino)-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-ylmethoxy]ethyl ester, ethyl 6-(4-tert-butyl-phenylsulphonyl-amino)-2-chloro-5-phenoxy-pyrimidin-3-carboxylate, 4-tert-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-methyl-2,2'-bipyrimidinyl-4-yl]-benzenesulphonamide, (S)-4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxymethyl)-2-morpholin-4-yl]-pyrimidin-4-yl]-benzenesulphonamide, (R)-4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxymethyl)-2-(morpholin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide, (S)-4-tert.-butyl-N-[5-(2-chloro-4-methoxy-phenoxy)-6-(2,3-dihydroxypropoxymethyl)-2-(morpholin-4-yl)-pyrimidin-4-yl]benzenesulphonamide, (R)-4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2,3-dihydroxy-propoxymethyl)-2-(morpholin-4-yl)-pyrimidin-4-yl]-benzenesulphonamide, (4S,5S)-4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(5-hydroxymethyl-2,2-dimethyl-1,3-dioxolan-4-ylmethoxymethyl)-pyrimidin-4-yl]-benzenesulphonamide, (2S,3S)-4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2,3,4-trihydroxybutoxymethyl)-4-yl]benzenesulphonamide, 6-(4-tert.-butyl-phenylsulphonamino)-5-(2-chloro-5-methoxy-phenoxy)-2,2'-bipyrimidinyl-4-carboxaldehyde, 4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-hydroxymethyl-2,2'-bipyrimidin-4-yl]-benzenesulphonamide, 4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-chloromethyl-2,2'-bipyrimidin-4-yl]-benzenesulphonamide, 4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxymethyl)-2,2'-bipyrimidin-4-yl]benzenesulphonamide, 4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-6-methoxy-2-methyl-pyrimidin-4-yl]-benzenesulphonamide, 4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2-formyl-6-methoxypyrimidin-4-yl]-benzenesulphonamide, 4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2-hydroxymethyl-6-methoxy-pyrimidin-4-yl]-benzenesulphonamide, 4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2-chloromethyl-6-methoxy-pyrimidin-4-yl]-benzenesulphonamide, 4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2-(2-hydroxy-ethoxymethyl-6-methoxy-pyrimidin-4-yl)]benzenesulphonamide, (RS)-4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2(2,2-dimethyl-1,3-dioxolan-4-ylmethoxymethyl)-6-methoxy-pyrimidin-4-yl]-benzenesulphonamide, (RS)-4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2(2,3-dihydroxy-propoxy-methyl)-6-methoxy-pyrimidin-4-yl]benzenesulphonamide, 4-tert.-butyl-N-[5-(2-chloro-5-methoxy-phenoxy)-2-amino-methyl-6-methoxy-pyrimidin-4-yl]-benzenesulphonamide, N-[5-(2-chloro-5-methoxy-phenoxy)-6-(2-methoxy-ethoxy)-2-methyl-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide, N-[5-(2-chloro-5-methoxy-phenoxy)-2-formyl-6-(2-methoxy-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide, N-[5-(2-chloro-5-methoxy-phenoxy)-2-hydroxy-

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methyl-6-(2-methoxy-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide, N-[5-(2-chloro-5-methoxy-phenoxy)-2-chloromethyl-6-(2-methoxy-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide, N-[5-(2-chloro-5-methoxy-phenoxy)-2-(2-hydroxy-ethoxymethyl)-6-(2-methoxy-ethoxy)-pyrimidin-4-yl]-1,3-benzodioxol-5-sulphonamide, 4-tert.-butyl-N-[6-methoxy-5-(2-methoxy-phenylsulphanyl)-methyl-pyrimidin-4-yl]-benzenesulphonamide, 4-tert.-butyl-N-[2-formyl-6-methoxy-5-(2-methoxy-phenylsulfonyl)-pyrimidin-4-yl]-benzenesulphonamide and 4-tert.-butyl-N-[2-hydroxymethyl-6-methoxy-5-(2-methoxy-phenylsulfonyl)-pyrimidin-4-yl]-benzenesulphonamide.

p. JOURNAL OF MEDICINAL CHEMISTRY 37(3):330 (1994)

10 Other compounds for use in the methods provided herein include those in the following tables:

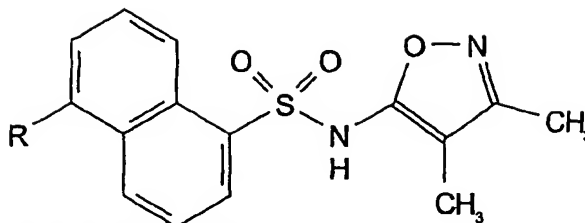


20	compd	heterocycle	R
	1	2-thiazolyl	4-NH ₂
	2	3,4-dimethyl-5-isoxazolyl	4-NH ₂
	3	3-methyl-5-isoxazolyl	4-NH ₂
25	4	3-pentyl-5-isoxazolyl	4-NH ₂
	5	3-phenyl-5-isoxazolyl	4-NH ₂
	6	3,4-dimethyl-5-isoxazolyl	4-NH(CH ₂) ₂ CH ₃
	2	3,4-dimethyl-5-isoxazolyl	4-OH
	8	3,4-dimethyl-5-isoxazolyl	4-NHCH ₂ C ₆ H ₆
	9	3,4-dimethyl-5-isoxazolyl	4-N(CH ₃) ₂
	30	10	3,4-dimethyl-5-isoxazolyl

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5



10

compd	R
11	$N(CH_3)_2$
12	$NHCOCH_3$
13	$CH_2N(CH_3)_2$
14	NH_2
15	$C(=CH_2)CH_3$
16	OCH_3
17	OH
18	CO_2H
19	H

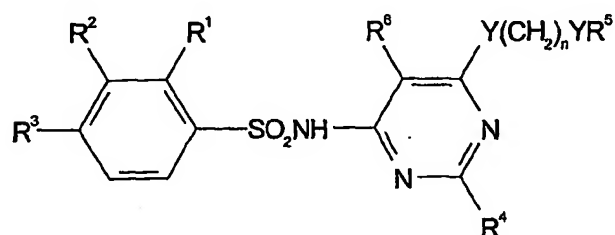
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q. European Patent Application Publication No. EP 0626 174 A2

Particular compounds for use in the methods provided herein include compounds represented by the formula:

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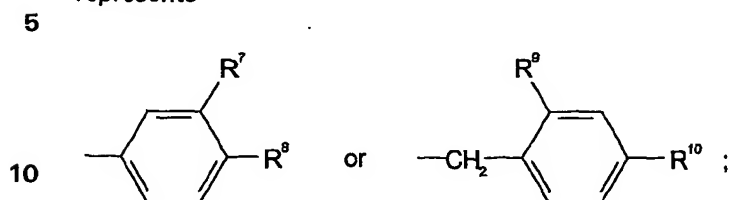
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or salts thereof, wherein R^1 represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halogen atom or a trifluoromethyl group; R^2 represents a halogen atom, a lower alkoxy group, a hydroxy-lower alkoxy group or a trifluoromethyl group; R^3 represents a hydroxyl group, a halogen atom, an alkylthio group, a cycloalkyl group, a hydroxy-lower alkyl group, a hydroxy-lower alkoxy group, hydroxyimino-lower alkyl group, a lower alkenyl group, an oxy-lower alkyl group, a trifluoromethyl group, a trifluoromethoxy group, a lower alkoxy group, a lower alkoxy-lower alkoxy group or an

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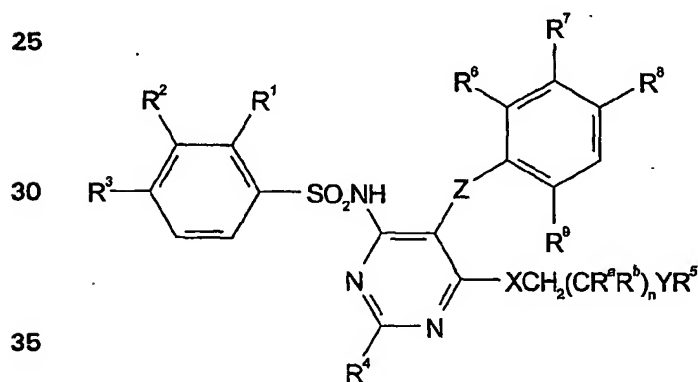
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aryl-lower alkoxy group, and R^2 and R^3 may form butadienyl; R^4 represents a lower alkyl group, an aryl group or heterocyclic aryl group; R^5 represents a lower alkanoyl group, a benzoyl group, a heterocyclic carbonyl group or a tetrahydropyran-2-yl group; R^6 represents



R^7 represents a lower alkoxy group or a nitro group; R^8 represents a halogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a nitro group, a hydroxyl group, an amino group or a trifluoromethyl group, and R^7 and R^8 may form butadienyl; R^9 represents a halogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group or a trifluoromethyl group; R^{10} represents a halogen atom, a lower alkyl group, a lower alkoxy group or a lower alkylthio group; X and Y each represent O, S or NH; and n represents 2, 3 or 4. In the above definition, "lower" means C_{1-7} .

Other compounds for use in the methods provided herein include compounds represented by the formula:



wherein R^1 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halogen atom or a trifluoromethyl group; R^2 represents a hydrogen atom, a halogen atom, a lower alkoxy group, a trifluoromethyl group or $-\text{OCH}_2\text{COOR}^a$; R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkylthio group, a trifluoromethyl group, a cycloalkyl group or a lower alkoxy

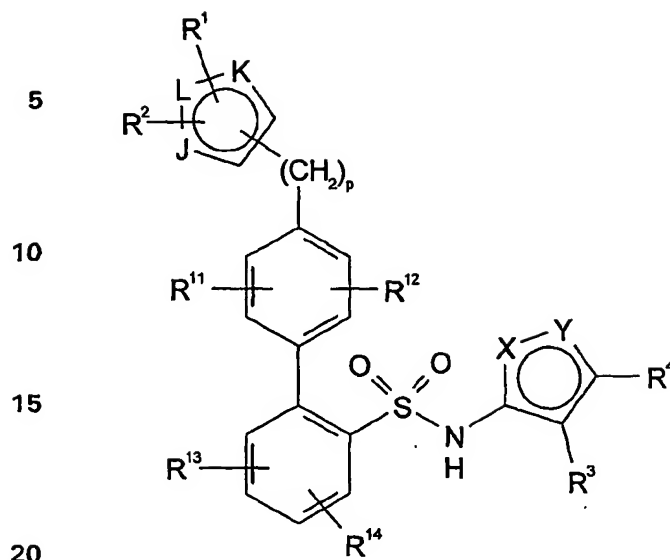
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group, and R² and R³ may form butadienyl, methylenedioxy, ethylenedioxy or isopropylidene; R⁴ represents a hydrogen atom, a lower alkyl group, a cycloalkyl group, a trifluoromethyl group, a lower alkoxy group, a lower alkylthio group, a lower alkylthio-lower alkyl group, a hydroxy-lower alkyl group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkyl group, hydroxy-lower alkoxy-lower alkyl group, hydroxy-lower alkoxy-lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a 2-methoxy-3-hydroxypropoxyl group, a 2-hydroxy-3-phenylpropyl group, an amino-lower alkyl group, a lower alkylamino-lower alkyl group, a di-lower alkylamino-lower alkylamino group, a lower alkylamino group, a di-lower alkylamino group, an arylamino group, an aryl group, an arylthio, an aryloxy group, an aryl-lower alkyl group or a heterocycle; R⁵ represents a hydrogen atom, a lower alkyl group, a lower alkanoyl group, a benzoyl group, a heterocyclic carbonyl group, a heterocyclic methyl group or a tetrahydropyrân-2-yl group; R⁶ to R⁹ each represent hydrogen atoms, halogen atoms, trifluoromethyl groups, lower alkyl groups, lower alkoxy groups, lower alkylthio groups, hydroxyl groups, hydroxymethyl groups, cyano groups, carboxyl groups, formyl groups, methylsulfinyl groups, methylsulfonyl groups, methylsulfonyloxy groups or lower alkoxycarbonyloxy groups; R⁷ may combine with R⁶ or R⁸ to form butadienyl, methylenedioxy, ethylenedioxy or isopropylidenedioxy; Z represent -O-, -S-, ethylene, vinylene, -CO-, -OCHR¹⁰ -or -SCHR¹⁰-, wherein R¹⁰ represents a hydrogen atom or a lower alkyl group; X and Y each represent O, S, or NH; YR⁵ represents a lower alkylsulfinyl group or -OCH₂CH(OR^c)CH₂-OR^d; R^a, R^b, R^c and R^d each represent hydrogen atoms or lower alkyl groups; R^c and R^d each represent methylene, ethylene or isopropylidene; and n represents 1, 2 or 3.

r. U.S. Patent No. 5,846,990

Compounds of the formula:

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its enantiomers and diastereomers, and pharmaceutically or veterinarily acceptable salts thereof are intended for use in the methods provided herein. In this embodiment, the

25 above symbols are defined as follows: one of X and Y is N and the other is O; R^1 , R^2 , R^3 and R^4 are each directly bonded to a ring carbon and are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1 , Z^2 and Z^3 ; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) $-C(O)H$ or $-C(O)R^5$; (h)

30 $-CO_2H$ or $-CO_2R^5$; (i) $-Z^4-NR^6R^7$; (j) $-Z^4-N(R^{10})-Z^5-NR^8R^9$; or (k) R^3 and R^4 together may also be alkylene or alkenylene, either of which may be substituted with Z^1 , Z^2 and Z^3 , completing a 4- to 8-membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached; R^5 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which

35 may be substituted with Z^1 , Z^2 and Z^3 ; R^6 , R^7 , R^8 , R^9 and R^{10} are each independently (a) hydrogen; or (b) alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; or R^6 and R^7 together may be alkylene or alkenylene, either of which may be substituted with Z^1 , Z^2 and Z^3 , completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which

40 they are attached; or any two of R^8 , R^9 and R^{10} together are alkylene or alkenylene, either of which may be substituted with Z^1 , Z^2 and Z^3 , completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; R^{11} ,

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- R^{12} , R^{13} and R^{14} are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1 , Z^2 and Z^3 , (c) heterocycle, substituted heterocycle or heterocycloxy; (d) halo; (e) hydroxyl; (f) cyano; (g) nitro; (h) $-C(O)H$ or $-C(O)R^5$; (i) $-CO_2H$ or $-CO_2R^5$; (j) $-SH$, $-S(O)_nR^5$, $-S(O)_m-OH$, $-S(O)_m-OR^5$, $-O-S(O)_m-OR^5$, $-O-S(O)_m-OH$ or $-O-S(O)_m-OR^5$; (k) $-Z^4-NR^6R^7$; or (l) $-Z^4-N(R^{10})-Z^5-NR^8R^9$; Z^1 , Z^2 and Z^3 are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkyl; (e) alkenyl; (f) aryl; (g) aralkyl; (h) alkoxy; (i) aryloxy; (j) aralkoxy; (k) heterocycle, substituted heterocycle or heterocycloxy; (l) $-SH$, $-S(O)_nZ^6$, $-S(O)_m-OH$, $-S(O)_m-OZ^6$, $-O-S(O)_m-Z^6$, $-O-S(O)_m-OH$ or $-O-S(O)_m-OZ^6$; (m) oxo; (n) nitro; (o) cyano; (p) $-C(O)H$ or $-C(O)Z^6$; (q) $-CO_2H$ or $-CO_2Z^6$; (r) $-Z^4-NZ^7Z^8$; (s) $-Z^4-N(Z^{11})-Z^5-H$; (t) $-Z^4-N(Z^{11})-Z^5-Z^6$; or (u) $-Z^4-N(Z^{11})-Z^5-NZ^7Z^8$; Z^4 and Z^5 are each independently (a) a single bond; (b) $-Z^9-S(O)_n-Z^{10}-$; (c) $-Z^9-C(O)-Z^{10}-$; (d) $-Z^9-C(S)-Z^{10}-$; (e) $-Z^9-O-Z^{10}-$; (f) $-Z^9-S-Z^{10}-$; (g) $-Z^9-O-C(O)-Z^{10}-$; or (h) $-Z^9-C(O)-O-Z^{10}-$; Z^6 is alkyl; alkyl substituted with one to three groups selected from halogen, aryl, aryloxy and alkoxy; alkenyl; alkynyl; cycloalkyl; cycloalkyl substituted with one to three groups selected from alkyl, aryl, alkenyl and alkoxyaryl; cycloalkyl to which is fused a benzene ring; aryloxy substituted with one or two halogens; cycloalkylalkyl; cycloalkenyl; cycloalkenylalkyl; aryl; aryl substituted with methylenedioxy or one to four groups selected from alkyl, dialkylamino, cyano, halogen, trihaloalkyl, alkoxy, trihaloalkoxy, dialkylaminocarbonyl, alkylcarbonylamino, arylalkoxy, aryloxyalkyl, alkylaryloxyalkyl and heterocycle; or heterocycle or substituted heterocycle; Z^7 and Z^8 are each independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, or Z^7 and Z^8 together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached; Z^9 and Z^{10} are each independently a single bond, alkylene, alkenylene or alkynylene; Z^{11} is (a) hydrogen; or (b) alkyl, alkyl substituted with one, two or three halogens, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl; or any two of Z^7 , Z^8 and Z^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; J is O, S, N or NR^{15} ; K and L are N or C, provided that at least one of K or L is C; R^{15} is hydrogen, alkyl, hydroxyethoxy methyl or methoxyethoxy methyl; each m is independently 1 or 2; each n is independently 0, 1 or 2; and p is 0 or an integer from 1 to 2.

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In this embodiment, it is preferred that at least one, or most preferably all, of the substituent groups are as follows: R¹ and R² are each independently hydrogen, alkyl, alkoxy, aryl, hydroxyalkyl, -CO₂ R⁵ or -Z⁴ -NR⁶ R⁷; R³ and R⁴ are each independently alkyl; and R¹¹, R¹², R¹³ and R¹⁴ are each independently hydrogen, hydroxy, amino,

5 heterocyclo, alkenyl, alkoxy, carboxamide or substituted lower alkyl.

Most preferred compounds of this embodiment are those wherein at least one, or most preferably all, of the substituent groups are as follows: R¹ and R² are each independently lower alkyl or hydrogen; R³ and R⁴ are each independently lower alkyl, especially methyl; and R¹², R¹³ and R¹⁴ are hydrogen and R¹¹ is hydrogen, hydroxy,

10 amino, heterocyclo, alkenyl, alkoxy, carboxamide or substituted lower alkyl.

Preferred compounds of this embodiment include N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-2,2,2-trifluoroacetamide; N-(3,4-Dimethyl-5-isoxazolyl)-2',4'-bis(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; (Z)-N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-(2-phenylethenyl)[1,1'-biphenyl]-2-sulfonamide; (E)-N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-(2-phenylethenyl)[1,1'-biphenyl]-2-sulfonamide; 4-Chloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)-[1,1'-biphenyl]-2-yl[methyl]phenylacetamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-oxazolyl-5-yl-4'-oxazol-2-yl-[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[2-(1-methylethyl)-5-oxazolyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-(4-oxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[2-(1-methylethyl)-4-oxazolyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[[5-(1-methylethyl)-2-oxazolyl]-methyl][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[[4-(1-methylethyl)-2-oxazolyl]-methyl][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[[2,2,2-trifluoroethyl)amino[methyl][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[[2,2,2-trifluoroethyl)amino[methyl][1,1'-biphenyl]-2-sulfonamide, monohydrochloride; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-(2,2,2-trifluoroethyl)-2,2-dimethylpropanamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-(2-oxazolylmethyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[methyl(2,2,2-trifluoroethyl)amino[methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, -trifluoroacetate (1:1); N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-3,3,3-trifluoro-N-methylpropanamide; N-[[2'-

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- [[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-4-fluoro-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-2-fluoro-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-3-fluoro-N-methylbenzamide; 4-Chloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylbenzamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[ethyl(2,2,2-trifluoroethyl)amino[methyl]-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; 2-Chloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylbenzamide; 2,4-Dichloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-3,4-difluoro-N-methylbenzamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[[[phenylmethyl](2,2,2-trifluoroethyl)amino[methyl]][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[[3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[[4-methoxyphenyl)methylamino[methyl]-4'-2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide, monohydrochloride; 2'-[[[3,3-Difluoro-1-pyrrolidinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide, monohydrochloride; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-pyrazinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,3-dimethyl-2-thiophenecarboxamide; 3-Cyano-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-2-methoxy-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-2-fluoro-N-methylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-1,3-benzodioxole-5-carboxamide; (R)-N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino]-sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]- α -methoxy-N-methylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-thiophenebutanamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-3,4,5-trifluoro-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-2,4,6-trifluoro-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-

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- oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-4-methoxy-N-methylbenzenepropanamide; 4-(1,1-Dimethylethyl)-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylcyclohexanecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-4-
- 5 (trifluoromethyl)-benzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-4-(trifluoromethoxy)benzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl][tetrahydro-N-methyl-2-furancarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-4-
- 10 pyridinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-3-pyridinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-pyridinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-1;2,3-thiadiazole-4-carboxamide; N-[[2'-
- 15 [[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,1,5-trimethyl-1H-pyrazole-3-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,3,5-trimethyl-4-isoxazolecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylbicyclo[4,2,0]octa-1,3,5-triene-7-
- 20 carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-3-methoxy-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-2,5-difluoro-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-3,5-difluoro-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-
- 25 isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-1-phenylcyclopropanecarboxamide; 3-(Dimethylamino)-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,2,2-trimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxamide; N-[[2'-
- 30 [[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-pyridineacetamide, trifluoroacetate (1:1); N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-4-pyridineacetamide, trifluoroacetate (1:1); N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-3-pyridineacetamide,

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- trifluoroacetate (1:1); N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,1-dimethyl-1H-indole-2-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-2,3,6-trifluoro-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-1,2,3,4-tetrahydro-N-methyl-2-naphthalene-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,2,4,6-tetramethylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-1,3-benzodioxole-5-acetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-4-(1-methylethoxy)benzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-2,3-dimethoxy-N-methylbenzamide; 1-(1,1-Dimethyl)-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)-amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,3-dimethyl-1H-pyrazole-5-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-3-(trifluoromethyl)benzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-4-fluoro-N-methyl-1-naphthalenecarboxamide; 3,5-Dichloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylbenzamide; 3,4-Dichloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-1-(4-methoxyphenyl)-N-methylcyclopropane-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-2,3,5,6-tetrafluoro-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-4-(trifluoromethyl)benzene-acetamide; 2,6-Dichloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)-amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl) [1,1'-biphenyl]-2-yl[methyl]-3-fluoro-N-methyl-5-(trifluoromethyl)benzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-4-fluoro-N-methyl-2-(trifluoromethyl) benzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-ethyl- α -phenylbenzeneacetamide; 2-(2-Chlorophenoxy)-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,2-dimethylpropanamide; 2-Chloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-3,4-dimethoxy-N-

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- methylbenzamide; 2-(2,4-Dichlorophenoxy)-N-[(2'-[(3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methylacetamide; 2-Chloro-N-[(2'-[(3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-5-(trifluoromethyl)benzamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[hydroxy(5-phenyl-2-oxazolyl)methyl]-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[(5-phenyl-2-oxazolyl)methyl][1,1'-biphenyl]-2-sulfonamide; 2'-[(2,2-Difluoro-2-phenylethyl)amino[methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide, monohydrochloride; N-(3,4-Dimethyl-5-isoxazolyl)-2'-(1H-imidazol-1-ylmethyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, monohydrochloride; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[(4-phenyl-1-piperazinyl)methyl][1,1'-biphenyl]-2-sulfonamide; N-[(2,3-Dihydro-1H-indol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, monohydrochloride; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[(2-phenyl-1H-imidazol-1-yl)methyl][1,1'-biphenyl]-2-sulfonamide, -monohydrochloride; 2'-[(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[(1,2,3,4-tetrahydro-1-quinolinyl)methyl][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(1-methylethyl)(2,2,2-trifluoroethyl)amino[methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[[[1-(trifluoromethyl)ethyl]amino[methyl]-[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[(3-phenyl-1H-pyrazol-1-yl)methyl][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-(1H-pyrazol-1-ylmethyl)-[1,1'-biphenyl]-2-sulfonamide; 2'-[(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,4-dimethyl-5-isoxazolyl)amino[methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-(2H-1,2,3-triazol-2-ylmethyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-(1H-1,2,3-triazol-1-ylmethyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-piperidinyl)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-[(2'-[(3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-phenoxyacetamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(4,4-dimethyl-3-oxo-2-isoxazolidinyl)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[2-(1-methylethyl)-1H-imidazol-1-yl[methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-

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- (2-oxazolyl)-2'-[(5-phenyl-2H-tetrazol-2-yl)methyl][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(5-methyl-1H-tetrazol-1-yl)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(5-methyl-2H-tetrazol-2-yl)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[(3-(trifluoromethyl)-1H-pyrazol-1-yl[methyl])[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3-(3-methyl-2-pyrazinyl)-1H-pyrazol-1-yl[methyl])-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3-(2-methyl-5-pyridinyl)-1H-pyrazol-1-yl[methyl])-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; 2'-[(1H-Benzotriazol-1-ylmethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[(1,2,3-triazolo[4,5-b]pyridinyl)methyl][1,1'-biphenyl]-2-sulfonamide, Isomers A and B; 2'-[(3,4-Dihydro-2H-pyrido[3,2-b]-1,4-oxazin-4-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[(imidazo[4,5b]-pyridinyl)methyl]-[1,1'-biphenyl]-2-sulfonamide, Isomers A and B; 2'-[(3,3-Difluoro-2,3-dihydro-2-oxo-1H-indol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(4-pyrimidinylamino)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(4-morpholinyl)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(4-methyl-1-piperazinyl)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; 1-Acetyl-4-[[2'-[(3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]piperazine; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[[4-(2,2,2-trifluoroethyl)-1-piperazinyl]-[methyl][1,1'-biphenyl]-2-sulfonamide dihydrochloride; N-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-1H-indole-2-carboxamide; N-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-2,3-dihydro-N-methyl-1H-indene-2-carboxamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[(1,2,3,4-tetrahydro-1-oxo-2-isoquinolinyl)methyl][1,1'-biphenyl]-2-sulfonamide; 2'-[(1H-Benzimidazol-1-ylmethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; 2'-[(2,3-Dihydro-2-oxo-3-benzoxazolyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; 2'-[(2,3-Dihydro-2-oxo-1H-indol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2'-[(4,4-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-[[2'-[(3,4-

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- Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,1,3-trimethyl-1H-pyrazole-5-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,2-dimethylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-1-ethyl-N,3-dimethyl-1H-pyrazole-5-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,1,3,5-tetramethyl-1H-pyrazole-4-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-2,6-difluoro-N-methylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-2-methoxy-N-methylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-3-methoxy-N-methylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-4-methoxy-N-methylbenzeneacetamide; 4-Chloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methylbenzeneacetamide; 2-Chloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-2,6-difluoro-N-methylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-3,5-difluoro-N-methylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-2,5-difluoro-N-methylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-2,4-difluoro-N-methylbenzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-4-quinolinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-6-benzothiazolecarboxamide; 3-(1,1-Dimethylethyl)-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,1-dimethyl-1H-pyrazole-5-carboxamide; 4-Chloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-2-methoxy-N-methylbenzamide; 3-(1,1-Dimethylethyl)-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-1-phenyl-1H-1,2,3-triazole-5-carboxamide; 2,3-Dihydro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,4-dimethyl-2-thioxo-3-thiazoleacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,3-dimethyl-5-(trifluoromethyl)-4-isoxazolecarboxamide; 3-(1,1-Dimethyl-

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- ethyl)-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-1-ethyl-N-methyl-1H-pyrazole-5-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-5-(1-pyrrolidinyl)-2H-tetrazole-2-acetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino-
- 5 [sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-3-(trifluoromethyl)-benzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)-[1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-(trifluoromethyl)benzeneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,1-dimethyl-1H-benzimidazole-2-propanamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino-
- 10 [sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,2-dimethyl-4-(trifluoromethyl)-3-pyridinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-5-(2-pyridinyl)-2-thiophenecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-4-phenyl-1,2,3-thiadiazole-5-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-
- 15 isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-4-(1,2,3-thiadiazol-4-yl)benzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-oxo-3(2H)-benzoxazolepropanamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,5-dimethyl-2-phenyl-4-oxazoleacetamide; N-[[2'-[[[3,4-Dimethyl-5-
- 20 isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-1,4-dithiaspiro[4.5]decane-8-carboxamide; 4-Chloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)-amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,1,3-trimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino-
- [sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-1-phenyl-5-propyl-1H-
- 25 pyrazole-4-acetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-3-[(4-methylphenoxy)methyl]benzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-5-[3-(trifluoromethyl)phenyl]-2H-tetrazole-2-acetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-
- 30 methyl-5-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,4-dimethyl-5-[3-(trifluoromethyl)phenyl]-5-thiazoleacetamide; 1-(4-Chlorophenyl)-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide; N-[[2'-[[[3,4-

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- Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,6-dimethyl-2-pyridinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-thiopheneacetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-(phenylmethoxy)benzeneacetamide; 3-(2-Chloro-6-fluorophenyl)-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,5-dimethyl-4-isoxazolecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,1-dimethyl-1H-pyrazole-4-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,5-dimethyl-1H-pyrazole-3-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-thiophenecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-3-thiophenecarboxamide; 6-Chloro-N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-3-pyridinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-1H-indole-5-carboxamide; 2-Chloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,6-dimethyl-4-pyridinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-4-cinnolinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-1H-indole-1-acetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-1H-indole-3-acetamide; 2,3-Dihydro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-1H-indene-2-acetamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-5-fluoro-N-methyl-1H-indole-2-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-3,5-dimethoxy-N-methylbenzamide; 5-Chloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-2-methoxy-N-methylbenzamide; 2,6-Dichloro-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N-methyl-3-pyridinecarboxamide; 3-(Acetylamino)-N-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,4-dimethylbenzamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl[methyl]-N,5-dimethyl-1-phenyl-1H-pyrazole-4-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-oxazolyl)[1,1'-

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- biphenyl]-2-yl[methyl]-4-methoxy-N-methyl-2-quinolinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl]amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N,5-dimethyl-2-phenyl-2H-1,2,3-triazole-4-carboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl]amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-phenoxo-3-pyridinecarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl]amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N',N'-diethyl-N-methyl-1,2-benzenedicarboxamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl]amino[sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-9H-fluorene-9-propanamide; 2'-[[[1-(1,1-Dimethylethyl)-3-methyl-1H-pyrazol-5-yl]amino[methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[[1H-pyrazol-3-ylamino)methyl][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[[1H-1,2,4-triazol-3-ylamino)methyl][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[[5-methyl-3-oxazolyl]amino[methyl]-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; 2'-[[[4-Cyano-1H-pyrazol-3-yl]amino[methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[[3,5-dimethyl-2-pyrimidinyl]amino[methyl]-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[[3,5-dimethyl-2-pyrimidinyl]amino[methyl]-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[[5-ethyl-1,3,4-thiadiazol-2-yl]amino[methyl]-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; 2'-[[[2-Benzothiazolylamino)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; 2'-[[[4-Bromo-1H-pyrazol-3-yl]amino[methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-2'-[[[5-(2-thienyl)-1H-pyrazol-3-yl]amino[methyl][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[[6-methoxy-2-benzothiazolyl]amino[methyl]-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; 2'-[[[4-(4-Chlorophenyl)-6-ethoxy-2-pyrimidinyl]amino[methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)][1,1'-biphenyl]-2-sulfonamide; and N-(4,5-dimethyl-3-isoxazolyl)-4'-(2-oxazolyl)-2'-[[[3-(trifluoromethyl)-1H-pyrazol-1-yl]methyl][1,1'-biphenyl]-2-sulfonamide.

s. **U.S. Patent No. 5,760,038**

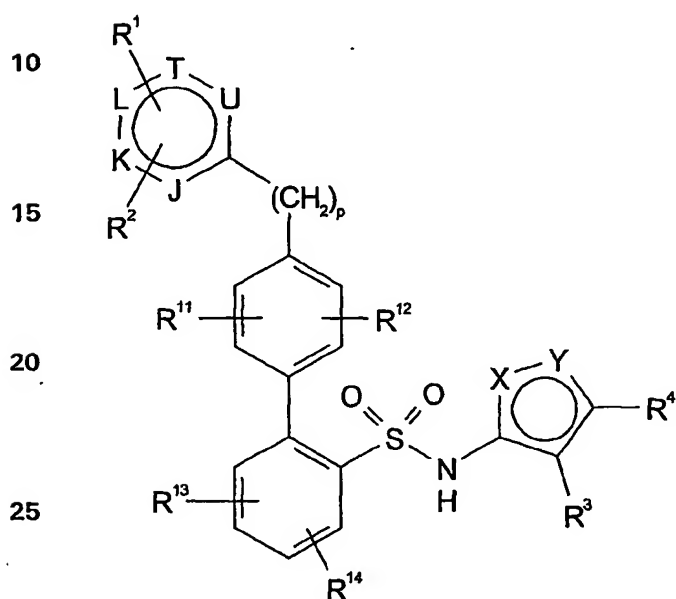
- 30 Other compounds for use in the methods provided herein include N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-pyrimidinyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-pyridinyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(3-pyridinyl)[1,1'-biphenyl]-2-sulfonamide; 4'-(4,6-Dimethoxy-2-pyrimidinyl)-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(4-

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pyrimidinyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-pyrazinyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(5-pyrimidinyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-4'-(2-pyridinyl)[1,1'-biphenyl]-2-sulfonamide, N^{4'}-oxide; and N-(3,4-Dimethyl-5-isoxazolyl)-4'-(6-methoxy-2-pyridinyl)[1,1'-biphenyl]-2-sulfonamide.

t. U.S. Patent No. 5,780,473

Compounds of the formula:



its enantiomers and diastereomers, and pharmaceutically or veterinarily acceptable salts thereof are also intended for use in the methods provided herein. In this embodiment, the above symbols are defined as follows: one of X and Y is N and the other is O; R¹ and R² are each directly bonded to a ring carbon and are each independently (a) hydrogen; (b) alkyl or alkoxy; (c) hydroxyl; (d) halo; or (e) amino; R³ and R⁴ are each directly bonded to a ring carbon and are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) -C(O)H or -C(O)R⁵; (h) -CO₂ H or -CO₂ R⁵; (i) -Z⁴ -NR⁶ R⁷; or (j) -Z⁴ -N(R¹⁰)-Z⁵ -NR⁸ R⁹; or (k) R³ and R⁴ together may also be alkylene or alkenylene, either of which may be substituted with Z¹, Z² and Z³, completing a 4- to

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- 8-membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached; R^5 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; R^6 , R^7 , R^8 , R^9 and R^{10} are each independently (a) hydrogen; or (b) alkyl,
- 5 cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; or R^8 and R^7 together may be alkylene or alkenylene, either of which may be substituted with Z^1 , Z^2 and Z^3 , completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached; or any two of R^8 , R^9 and R^{10} together are alkylene or alkenylene, either of
- 10 which may be substituted with Z^1 , Z^2 and Z^3 , completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; R^{11} , R^{12} , R^{13} and R^{14} are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1 , Z^2 and Z^3 , (c) heterocycle,
- 15 substituted heterocycle or heterocycloxy; (d) halo; (e) hydroxyl; (f) cyano; (g) nitro; (h) $-C(O)H$ or $-C(O)R^5$; (i) $-CO_2H$ or $-CO_2R^5$; (j) $-SH$, $-S(O)_nR^5$, $-S(O)_m-OH$, $-S(O)_m-OR^5$, $-O-S(O)_m-OR^5$, $-O-S(O)_mOH$ or $-O-S(O)_m-OR^5$; (k) $-Z^4-NR^6R^7$; or (l) $-Z^4-N(R^{10})-Z^5-NR^8R^9$; Z^1 , Z^2 and Z^3 are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkyl; (e) alkenyl; (f) aryl; (g) aralkyl; (h) alkoxy; (i) aryloxy; (j) aralkoxy; (k)
- 20 heterocycle, substituted heterocycle or heterocycloxy; (l) $-SH$, $-S(O)_nZ^6$, $-S(O)_m-OH$, $-S(O)_m-OZ^6$, $-O-S(O)_m-Z^6$, $-O-S(O)_mOH$ or $-O-S(O)_m-OZ^6$; (m) oxo; (n) nitro; (o) cyano; (p) $-C(O)H$ or $-C(O)Z^6$; (q) $-CO_2H$ or $-CO_2Z^6$; (r) $-Z^4-NZ^7Z^8$; (s) $-Z^4-N(Z^{11})-Z^5-H$; (t) $-Z^4-N(Z^{11})-Z^5-Z^6$; or (u) $-Z^4-N(Z^{11})-Z^5-NZ^7Z^8$; Z^4 and Z^5 are each independently (a) a single bond; (b) $-Z^9-S(O)_n-Z^{10}-$; (c) $-Z^9-C(O)-Z^{10}-$; (d)
- 25 $-Z^9-C(S)-Z^{10}-$; (e) $-Z^9-O-Z^{10}-$; (f) $-Z^9-S-Z^{10}-$; (g) $-Z^9-O-C(O)-Z^{10}-$; or (h) $-Z^9-C(O)-O-Z^{10}-$; Z^6 is alkyl; alkyl substituted with one to three groups selected from halogen, aryl, aryloxy and alkoxy; alkenyl; alkynyl; cycloalkyl; cycloalkyl substituted with one to three groups selected from alkyl, aryl, alkenyl and alkoxyaryl; cycloalkyl to which is fused a benzene ring; aryloxy substituted with one or two halogens;
- 30 cycloalkylalkyl; cycloalkenyl; cycloalkenylalkyl; aryl; aryl substituted with methylenedioxy or one to four groups selected from alkyl, dialkylamino, cyano, halogen, trihaloalkyl, alkoxy and trihaloalkoxy; or heterocyclo or substituted heterocyclo; Z^7 and Z^8 are each independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, or Z^7 and Z^8

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together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached; Z⁹ and Z¹⁰ are each independently a single bond, alkylene, alkenylene or alkynylene; Z¹¹ is (a) hydrogen; or (b) alkyl, alkyl substituted with one, two or three halogens, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl; or any two of Z⁷, Z⁸ and Z¹¹ together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; J, K, L, T and U are each independently N or C, provided that at least one is N, and at most two are N; and when only one of J, K, L, T and U is N, the N may be substituted with -O⁹ so that an N-oxide is formed; each m is independently 1 or 2; each n is independently 0, 1 or 2; and p is 0 or an integer from 1 to 2.

In this embodiment, it is preferred that the heterocyclic ring containing U, T, L, K and J is a pyridine (such as a 2- or 3-pyridine), pyrimidine (such as a 2-, 4- or 5-pyrimidine), or pyrazine (such as a 2-pyrazine) ring; R¹ and R² are each independently hydrogen, alkyl or alkoxy; R³ and R⁴ are each independently alkyl; R¹¹, R¹², R¹³ and R¹⁴ are each hydrogen, -CHO or substituted alkyl, especially where R¹², R¹³ and R¹⁴ are each hydrogen and R¹¹ is alkyl substituted with heterocycle, substituted heterocycle or -Z⁴-N(Z¹¹)-Z⁵-Z⁶; and p is 0.

Most preferred compounds of this embodiment are those wherein: the heterocyclic ring containing U, T, L, K and J is a 2-pyrimidine ring; R¹ and R² are each independently lower alkoxy or hydrogen; and R³ and R⁴ are each independently lower alkyl, especially methyl.

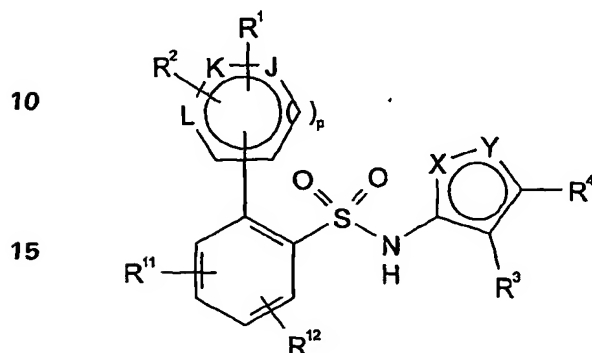
Preferred compounds of this embodiment include N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino]-sulfonyl]-4-(2-pyrimidinyl)][1,1'-biphenyl]-2-yl[methyl]-N-methyl-2-thiophenebutanamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[[[4-methoxyphenyl)methylamino[methyl]-4'-(2-pyrimidinyl)][1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-formyl-4'-(2-pyrimidinyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(methylamino)methyl]-4'-(2-pyrimidinyl)[1,1'-biphenyl]-2-sulfonamide; N-[[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino[sulfonyl]-4-(2-pyridinyl)][1,1'-biphenyl]-2-yl[methyl]-N,3,3-trimethylbutanamide; N-(4,5-Dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-(2-pyrimidinyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-(2-pyrimidinyl)[1,1'-biphenyl]-2-sulfonamide; N-[[2'-[[[4,5-Dimethyl-3-isoxazolyl)amino]-sulfonyl]-4'-(2-pyrimidinyl)][1,1'-biphenyl]-2-yl[methyl]-N,3,3-trimethylbutanamide; N-

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(4,5-Dimethyl-3-isoxazolyl)-4'-(2-pyrimidinyl)-2'-[[3-(trifluoromethyl)-1H-pyrazol-1-yl[methyl]][1,1'- biphenyl]-2-sulfonamide; and N-(3,4-Dimethyl-5-isoxazolyl)-41-(2-pyrimidinyl)-2'-[[3-(trifluoromethyl)-1H-pyrazol-1-yl[methyl]][1,1'- biphenyl]-2-sulfonamide.

5 u. U.S. Patent No. 5,939,446

Compounds of the formula:



20 its enantiomers and diastereomers, and pharmaceutically or veterinarily acceptable salts thereof are intended for use in the methods provided herein. In this embodiment, the above symbols are defined as follows: one of X and Y is N and the other is O; R¹, R², R³ and R⁴ are each directly bonded to a ring carbon and are each independently (a)

25 hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) -C(O)H or -C(O)R⁵; (h) -CO₂H or -CO₂R⁵; (i) -Z⁴-NR⁶R⁷; (j) -Z⁴-N(R¹⁰)-Z⁵-NR⁸R⁹; or (k) R³ and R⁴ together may also be alkylene or alkenylene, either of which may be substituted with Z¹, Z² and Z³,

30 completing a 4- to 8-membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached; R⁵ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z¹, Z² and Z³; R⁶, R⁷, R⁸, R⁹ and R¹⁰ are each independently (a) hydrogen; or (b) alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, any

35 of which may be substituted with Z¹, Z² and Z³; or R⁶ and R⁷ together may be alkylene or alkenylene, either of which may be substituted with Z¹, Z² and Z³, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached; or any two of R⁸, R⁹ and R¹⁰ together are alkylene or alkenylene, either of which may be substituted with Z¹, Z² and Z³, completing a 3- to 8-membered

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- saturated or unsaturated ring together with the atoms to which they are attached; R^{11} and R^{12} are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1 , Z^2 and Z^3 , (c) heterocycle,
- 5 substituted heterocycle or heterocyclooxy; (d) halo; (e) hydroxyl; (f) cyano; (g) nitro; (h) $-C(O)H$ or $-C(O)R^5$; (i) $-CO_2H$ or $-CO_2R^5$; (j) $-SH$, $-S(O)_nR^5$, $-S(O)_m-OH$, $-S(O)_m-OR^5$, $-O-S(O)_m-OR^5$, $-O-S(O)_mOH$ or $-O-S(O)_m-OR^5$; (k) $-Z^4-NR^6R^7$; or (l) $-Z^4-N(R^{10})-Z^5-NR^6R^9$; Z^1 , Z^2 and Z^3 are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkyl; (e) alkenyl; (f) aryl; (g) aralkyl; (h) alkoxy; (i) aryloxy; (j) aralkoxy; (k) heterocycle,
- 10 substituted heterocycle or heterocyclooxy; (l) $-SH$, $-S(O)_nZ^6$, $-S(O)_m-OH$, $-S(O)_m-OZ^6$, $-O-S(O)_m-Z^6$, $-O-S(O)_mOH$ or $-O-S(O)_m-OZ^6$; (m) oxo; (n) nitro; (o) cyano; (p) $-C(O)H$ or $-C(O)Z^6$; (q) $-CO_2H$ or $-CO_2Z^6$; (r) $-Z^4-NZ^7Z^8$; (s) $-Z^4-N(Z^{11})-Z^5-H$; (t) $-Z^4-N(Z^{11})-Z^5-Z^6$; or (u) $-Z^4-N(Z^{11})-Z^5-NZ^7Z^8$; Z^4 and Z^5 are each independently (a) a single bond; (b) $-Z^9-S(O)_n-Z^{10}-$; (c) $-Z^9-C(O)-Z^{10}-$; (d) $-Z^9-C(S)-Z^{10}-$; (e) $-Z^9-O-Z^{10}-$; (f) $-Z^9-S-Z^{10}-$; (g) $-Z^9-O-C(O)-$
- 15 $Z^{10}-$; or (h) $-Z^9-C(O)-O-Z^{10}-$; Z^6 is alkyl; alkyl substituted with one to three groups selected from halogen, aryl, aryloxy and alkoxy; alkenyl; alkynyl; cycloalkyl; cycloalkyl substituted with one to three groups selected from alkyl, aryl, alkenyl and alkoxyaryl; cycloalkyl to which is fused a benzene ring; aryloxy substituted with one or two halogens; cycloalkylalkyl; cycloalkenyl; cycloalkenylalkyl; aryl; aryl substituted with
- 20 methylenedioxy or one to four groups selected from alkyl, dialkylamino, cyano, halogen, trihaloalkyl, alkoxy and trihaloalkoxy; or heterocycle or substituted heterocycle; Z^7 and Z^8 are each independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, or Z^7 and Z^8 together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they
- 25 are attached; Z^9 and Z^{10} are each independently a single bond, alkylene, alkenylene or alkynylene; Z^{11} is (a) hydrogen; or (b) alkyl, alkyl substituted with one, two or three halogens, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl; or any two of Z^7 , Z^8 and Z^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; each m is
- 30 independently 1 or 2; each n is independently 0, 1 or 2; p is 0 or 1; and when p is 0, then J is N, NR^{13} or S; K and L are each $-C$; R^{13} is H, alkyl or $-SO_2R^{14}$; and R^{14} is aryl; and R^1 and R^2 together may also be alkylene or alkenylene, either of which may be substituted with Z^1 , Z^2 and Z^3 , completing a 4- to 8-membered saturated, unsaturated or aromatic ring together with the atoms to which they are attached; or when p is 1, then

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J, K and L are each, independently, -C or N, provided that at least one of J, K and L is -C and at least one of J, K and L is N.

In this embodiment, it is preferred that at least one, or most preferably all, of the substituent groups are as follows: X is O and Y is N; R³ and R⁴ are each independently
5 alkyl, most preferably, methyl; R¹¹ and R¹² are each independently hydrogen, hydroxy, amino, alkenyl, carboxamide or substituted lower alkyl, most preferably, hydrogen; when p is 0, then J is N or NR¹³, most preferably, where R¹³ is hydrogen or phenylsulfonyl, and R¹ and R² together are alkenylene, completing a 6-membered aromatic ring; or J is S, and R¹ and R² are hydrogen; and when p is 1, then R¹ and R²
10 are each independently hydrogen, alkyl, alkoxy, aryl, hydroxyalkyl, -CO₂ R⁵ or -Z⁴ -NR⁸ R⁷, most preferably, hydrogen.

Preferred compounds of this embodiment include N-(3,4-Dimethyl-5-isoxazolyl)-2-(2-thienyl)benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-(3-thienyl)benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-(2-pyridinyl)benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-[1-(phenylsulfonyl)-1H-indol-3-yl]benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-(1H-indol-3-yl)benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-[1-(phenylsulfonyl)-1H-indol-2-yl]benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-(2-pyrimidinyl)benzenesulfonamide; N-(3,4-Dimethyl-5-isoxazolyl)-2-(3-pyridinyl)benzenesulfonamide; and N-(3,4-Dimethyl-5-isoxazolyl)-2-(1H-indol-2-yl)benzenesulfonamide.

v. U.S. Patent No. 5,827,869

Compounds of the formula:

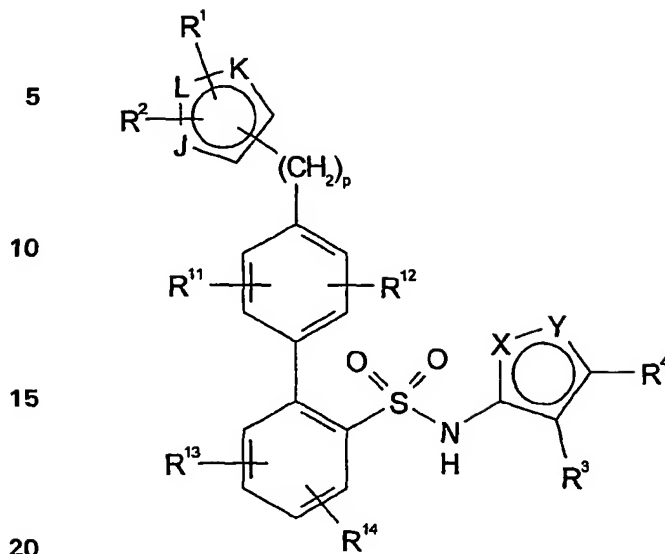
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its enantiomers and diastereomers, and pharmaceutically or veterinarily acceptable salts thereof are intended for use in the methods provided herein. In this embodiment, the
 25 above symbols are defined as follows: one of X and Y is N and the other is O; R¹, R², R³ and R⁴ are each directly bonded to a ring carbon and are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) -C(O)H or -C(O)R⁵; (h)
 30 -CO₂H or -CO₂R⁵; (i) -Z⁴-NR⁶R⁷; (j) -Z⁴-N(R¹⁰)-Z⁵-NR⁸R⁹; or (k) R³ and R⁴ together may also be alkylene or alkenylene, either of which may be substituted with Z¹, Z² and Z³, completing a 4- to

8-membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached; R⁵ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl,
 35 cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z¹, Z² and Z³; R⁶, R⁷, R⁸, R⁹ and R¹⁰ are each independently (a) hydrogen; or (b) alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z¹, Z² and Z³; or R⁶ and R⁷ together may be alkylene or alkenylene, either of which may be substituted with Z¹, Z² and Z³, completing a 3- to 8-membered
 40 saturated or unsaturated ring together with the nitrogen atom to which they are attached; or any two of R⁸, R⁹ and R¹⁰ together are alkylene or alkenylene, either of which may be substituted with Z¹, Z² and Z³, completing a 3- to 8-membered saturated

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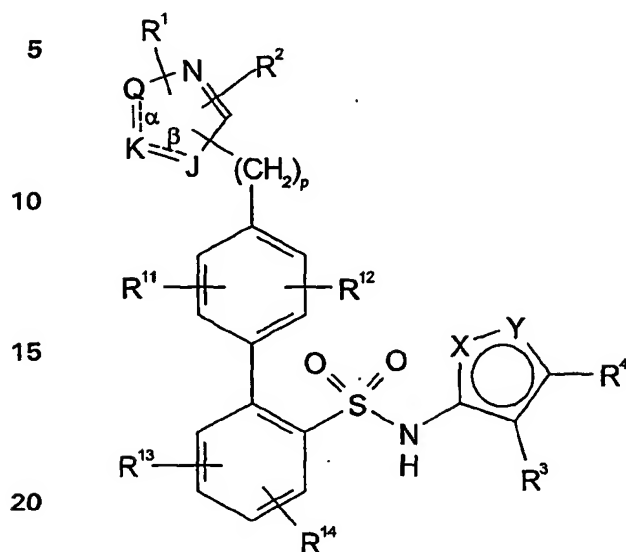
- or unsaturated ring together with the atoms to which they are attached; R^{11} , R^{12} , R^{13} and R^{14} are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1 , Z^2 and Z^3 , (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) $-C(O)H$ or $-C(O)R^5$; (h) $-C_2H$ or $-CO_2R^5$; (i) $-SH$, $-S(O)_nR^5$, $-S(O)_m-OH$, $-S(O)_m-OR^5$, $-O-S(O)_m-OR^5$, $-O-S(O)_mOH$ or $-O-S(O)_m-OR^5$; (j) $-Z^4-NR^6R^7$; or (k) $-Z^4-N(R^{10})-Z^5-NR^8R^9$; Z^1 , Z^2 and Z^3 are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkyl; (e) alkenyl; (f) aralkyl; (g) alkoxy; (h) aryloxy; (i) aralkoxy; (j) $-SH$, $-S(O)_nZ^6$, $-S(O)_m-OH$, $-S(O)_m-OZ^6$, $-O-S(O)_m-Z^6$, $-O-S(O)_mOH$ or $-O-S(O)_m-OZ^6$; (k) oxo; (l) nitro; (m) cyano; (n) $-C(O)H$ or $-C(O)Z^6$; (o) $-CO_2H$ or $-CO_2Z^6$; (p) $-Z^4-NZ^7Z^8$; (q) $-Z^4-N(Z^{11})-Z^5-H$; (r) $-Z^4-N(Z^{11})-Z^5-Z^6$; or (s) $-Z^4-N(Z^{11})-Z^5-NZ^7Z^8$; Z^4 and Z^5 are each independently (a) a single bond; (b) $-Z^9-S(O)_n-Z^{10}-$; (c) $-Z^9-C(O)-Z^{10}-$; (d) $-Z^9-C(S)-Z^{10}-$; (e) $-Z^9-O-Z^{10}-$; (f) $-Z^9-S-Z^{10}-$; (g) $-Z^9-O-C(O)-Z^{10}-$; or (h) $-Z^9-C(O)-O-Z^{10}-$; Z^6 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl; Z^7 and Z^8 are each independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, or Z^7 and Z^8 together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached; Z^9 and Z^{10} are each independently a single bond, alkylene, alkenylene or alkynylene; Z^{11} is (a) hydrogen; or (b) alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl; or any two of Z^7 , Z^8 and Z^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; J is O, S, N or NR^{15} ; K and L are N or C, provided that at least one of K or L is C; R^{15} is hydrogen, alkyl, hydroxyethoxy methyl or methoxyethoxy methyl; each m is independently 1 or 2; each n is independently 0, 1 or 2; and p is 0 or an integer from 1 to 2.

In this embodiment, it is preferred that: R^1 and R^2 are each independently hydrogen, alkyl, alkoxy, aryl, hydroxyalkyl, $-CO_2R^5$ or $-Z^4-NR^6R^7$; R^3 and R^4 are each independently alkyl; and R^{11} and R^{12} are each independently hydrogen, hydroxy, amino or substituted lower alkyl. Most preferred compounds of this embodiment are those wherein: R^1 and R^2 are each independently lower alkyl or hydrogen; R^3 and R^4 are each independently lower alkyl, especially methyl; and R^{11} and R^{12} are each independently hydrogen, hydroxy or substituted lower alkyl.

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w. U.S. Patent No. 5,846,985

Compounds of the formula:



its enantiomers and diastereomers, and pharmaceutically or veterinarily acceptable salts thereof are intended for use in the methods provided herein. In this embodiment, the above symbols are defined as follows: one of X and Y is N and the other is O; Q is N or NR¹⁵; J is O, S, N or NR¹⁵; K is C=O or CH; the dotted line α between Q and K denotes an optional double bond when Q is N and K is CH; the dotted line β between K and J denotes an optional double bond when K is CH and J is N; with the proviso that said α and β double bonds may not simultaneously be present; R¹ and R², when present, and R³ and R⁴, are each directly bonded to a ring carbon and are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) -C(O)H or -C(O)R⁵; (h) -CO₂H or -CO₂R⁵; (i) -Z⁴-NR⁸R⁷; or (j) -Z⁴-N(R¹⁰)-Z⁵-NR⁸R⁹; and (k) R³ and R⁴ together may also be alkylene or alkenylene, either of which may be substituted with Z¹, Z² and Z³, completing a 4- to 8-membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached; R⁵ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z¹, Z² and Z³; R⁶, R⁷, R⁸, R⁹ and R¹⁰ are each independently (a) hydrogen; or (b) alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z¹, Z² and Z³; or R⁶ and R⁷ together may be alkylene

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or alkenylene, either of which may be substituted with Z^1 , Z^2 and Z^3 , completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they are attached; or any two of R^8 , R^9 and R^{10} together are alkylene or alkenylene, either of which may be substituted with Z^1 , Z^2 and Z^3 , completing a 3- to 8-membered

5 saturated or unsaturated ring together with the atoms to which they are attached; R^{11} , R^{12} , R^{13} and R^{14} are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted with Z^1 , Z^2 and Z^3 , (c) heterocyclo, substituted heterocyclo or heterocyclooxy; (d) halo; (e) hydroxyl; (f) cyano; (g) nitro; (h)

10 $-C(O)H$ or $-C(O)R^5$; (i) $-CO_2H$ or $-CO_2R^5$; (j) $-SH$, $-S(O)nR^5$, $-S(O)m-OH$, $-S(O)m-OR^5$, $-O-S(O)m-OR^5$, $-O-S(O)mOH$ or $-O-S(O)m-OR^5$; (k) $-Z^4-NR^6R^7$; or (l) $-Z^4-N(R^{10})-Z^5-NR^8R^9$; Z^1 , Z^2 and Z^3 are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkyl; (e) alkenyl; (f) aryl; (g) aralkyl; (h) alkoxy; (i) aryloxy; (j) aralkoxy; (k) heterocyclo, substituted heterocyclo or heterocyclooxy; (l) $-SH$, $-S(O)_nZ^6$, $-S(O)_m-OH$,

15 $-S(O)_m-OZ^6$, $-O-S(O)m-Z^6$, $-O-S(O)_mOH$ or $-O-S(O)_m-OZ^6$; (m) oxo; (n) nitro; (o) cyano; (p) $-C(O)H$ or $-C(O)Z^6$; (q) $-CO_2H$ or $-CO_2Z^6$; (r) $-Z^4-NZ^7Z^8$; (s) $-Z^4-N(Z^{11})-Z^5-H$; (t) $-Z^4-N(Z^{11})-Z^5-Z^8$; or (u) $-Z^4-N(Z^{11})-Z^5-NZ^7Z^8$; Z^4 and Z^5 are each independently (a) a single bond; (b) $-Z^9-S(O)_n-Z^{10}-$; (c) $-Z^9-C(O)-Z^{10}-$; (d) $-Z^9-C(S)-Z^{10}-$; (e) $-Z^9-O-Z^{10}-$; (f) $-Z^9-S-Z^{10}-$; (g) $-Z^9-O-C(O)-Z^{10}-$; or (h)

20 $-Z^9-C(O)-Z^{10}-$; Z^6 is alkyl; alkyl substituted with one to three groups selected from halogen, aryl, aryloxy and alkoxy; alkenyl; alkynyl; cycloalkyl; cycloalkyl substituted with one to three groups selected from alkyl, aryl, alkenyl and alkoxyaryl; cycloalkyl to which is fused a benzene ring; aryloxy substituted with one or two halogens; cycloalkylalkyl; cycloalkenyl; cycloalkenylalkyl; aryl; aryl substituted with

25 methylenedioxy or one to four groups selected from alkyl, dialkylamino, cyano, halogen, trihaloalkyl, alkoxy and trihaloalkoxy; or heterocyclo or substituted heterocyclo; Z^7 and Z^8 are each independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl or Z^7 and Z^8 together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atom to which they

30 are attached; Z^9 and Z^{10} are each independently a single bond, alkylene, alkenylene or alkynylene; Z^{11} is (a) hydrogen; or (b) alkyl, alkyl substituted with one, two or three halogens, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl; or any two of Z^7 , Z^8 and Z^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; R^{15} is

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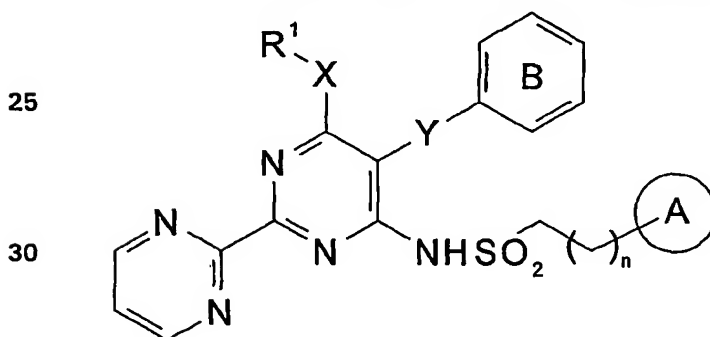
hydrogen, alkyl, hydroxyethoxy methyl or methoxyethoxy methyl; each m is independently 1 or 2; each n is independently 0, 1 or 2; and p is 0 or an integer from 1 to 2.

Preferred compounds of this embodiment are those having one or more (most preferably, all) of the following preferred substituent definitions: X is O; Y is N; R³ and R⁴ are alkyl, especially lower alkyl such as methyl; R¹¹, R¹², R¹³ and R¹⁴ are each independently hydrogen, hydroxy, amino, heterocyclo, alkenyl, alkoxy, carboxamide, or substituted lower alkyl, especially, R¹², R¹³ and R¹⁴ are hydrogen and R¹¹ is hydrogen, hydroxy, amino, heterocyclo, alkenyl, alkoxy, carboxamide or substituted lower alkyl; p is zero; R¹ and R² are hydrogen or are absent; Q is N; K is CH, J is O and the double bond α is present or K is C=O, J is NR¹⁵ and neither of the double bonds α or β is present; R¹⁵ is hydrogen, hydroxyethoxy methyl or methoxyethoxy methyl.

Preferred compounds of this embodiment include 4'-[4,5-dihydro-4-[(2-methoxyethoxy)methyl]-5-oxo-1H-1,2,4-triazol-1-yl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide; 4'-[4,5-dihydro-4-[(2-hydroxyethoxy)methyl]-5-oxo-1H-1,2,4-triazol-1-yl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-4'-(1,3,4-oxadiazol-2-yl)[1,1'-biphenyl]-2-sulfonamide; and salts thereof.

x. International Patent Application Publication No. WO 98/57938

Also intended for use in the methods provided herein are compounds of formula:



and pharmaceutically acceptable salts thereof, where n is 1 or 2; A represents an optionally substituted aryl group or an optionally substituted heteroaryl group; B represents an optionally substituted phenyl group; R¹ represents a lower alkyl, lower alkenyl, or lower alkynyl group (these groups each being optionally substituted by one to three groups selected from the group consisting of halogen atoms and hydroxy, lower

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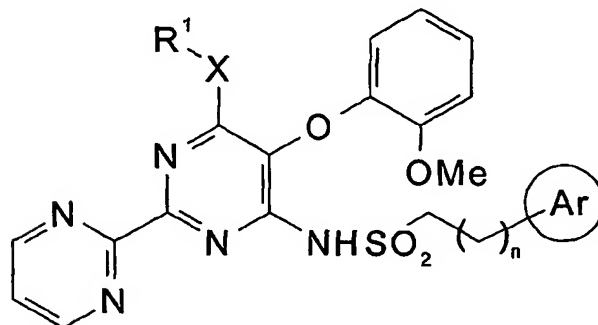
alkyl-O-, carboxyl, lower alkyl-O-CO-, and cycloalkyl groups); X represents a group represented by O, S, or -NH-; and Y represents O or S.

Preferred compounds of this embodiment are those shown in the following tables:

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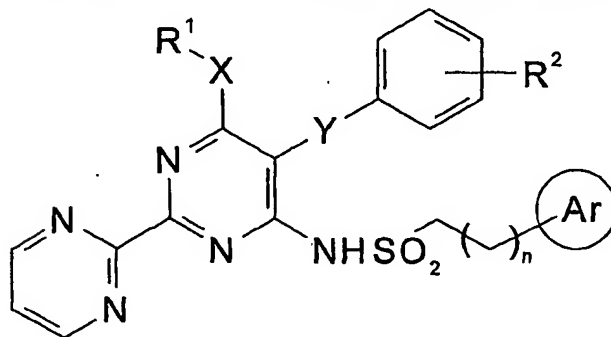
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R¹X-	n	Ar
MeO-	1	Ph
MeO-(CH₂)₂-O-	1	Ph
MeO-	1	2,4,6-triMe-Ph
HO-(CH₂)₂-O-	1	2,4,6-triMe-Ph
MeO-	1	1-Naph
MeO-	1	2-Naph
MeO-	1	4-MePh
MeO-	1	2-Th
MeO-	2	Ph

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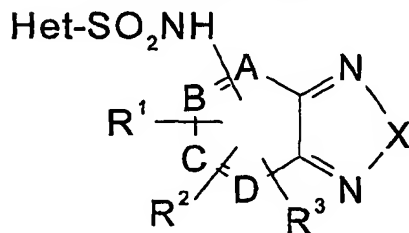


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	R ¹ X-	-Y-	-R ²	-R ³	n	Ar
	MeO-	O	2-MeO-	H	1	2,6-Di-Me-Ph
	MeO-	O	2-MeO-	H	1	2-Cl-Ph
	MeO-	O	2-MeO-	H	1	4-MeO-Ph
5	MeO-	O	2-MeO-	H	1	2,4-Di-Me-Ph
	MeO-	O	2-MeO-	H	1	3-Th
	MeO-	O	2-MeO-	H	1	3-Py
	MeO-	O	2-MeO-	H	1	4-Py
	FCH ₂ CH ₂ O-	O	2-MeO-	H	1	Ph
10	HC≡C-O-	O	2-MeO-	H	1	Ph
	MeO-	O	2-MeO-	H	1	Ph
	MeO-	O	2-MeO-	H	1	Ph
	MeS-	O	2-MeO-	H	1	Ph
	MeNH-	O	2-MeO-	H	1	Ph
15	MeOCH ₂ CH ₂ O-	O	2-MeO-	H	1	2-Th
	MeOCH ₂ CH ₂ O-	O	2-MeO-	H	1	2-Py
	MeO-	O	2-MeO-	H	1	2-Py
	MeO-	O	2-MeO-	H	2	2-Th
	MeO-	O	2-MeO-	H	2	2-Py
20	MeOCH ₂ CH ₂ O-	O	2-MeO-	H	2	Ph
	FCH ₂ CH ₂ O-	O	2-MeO-	H	2	Ph
	HC≡C-O-	O	2-MeO-	H	2	Ph

y. International Patent Application Publication No. WO 97/30996

25 Compounds of formula:



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and their salts, are intended for use in the methods provided herein. In this embodiment, -A=B=C=D- is a -CH=CH-CH=CH- group in which 1 or 2 of the CH groups may be replaced with N; Het is an unsubstituted or -Z-R⁶ substituted mono- or bicyclic saturated, unsaturated or aromatic heterocycle containing from 1 to 4 N, O and/or S atoms; R¹, R² and R³ are each independently H, Hal, A, CF₃, NO₂, NR⁴R⁵, CN, COOR⁴ or NHCOR⁴; R⁴ and R⁵ are each independently H or A, or together form -CH₂-(CH₂)_n-CH₂-; R⁶ is an unsubstituted or a mono, di or trisubstituted phenyl, benzothiadiazol-5-yl or benzoxadiazol-5-yl group, where the substituents are R⁷, R⁸ and/or R⁹; R⁷, R⁸ and R⁹ are each independently A, O-A, CN, COOH, COOA, Hal, formyl, -CO-A, benzothiadiazol-5yl or benzoxadiazol-5-yl, or R⁷ and R⁸ together form -O-(CH₂)_m-O-; A is C₁₋₈alkyl; X is O or S; Z is -CO-, -CONH-, -CO-(CH₂)_n-, -CH=CH-, -(CH₂)_n-, -CONHCO-, -NHCONH-, -NHCOO-, -O-CONH-, -CO-O- or -O-CO-; Hal is F, Cl, Br, or I; m is 1 or 2; and n is 1, 2, or 3.

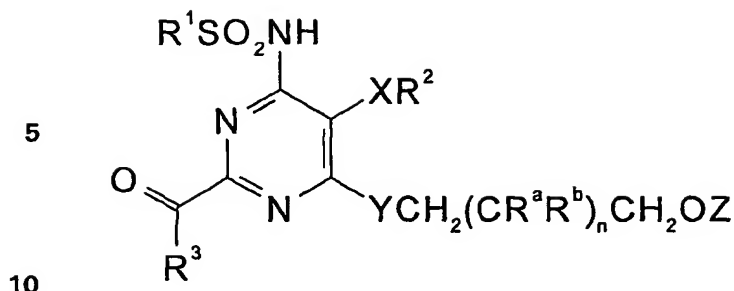
Preferred compounds of this embodiment include 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-N-(6-acetyl-1,3-benzodioxol-5-yl)thiophene-2-carboxamide; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-N-(6-cyano-1,3-benzodioxol-5-yl)thiophene-3-carboxamide; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-2-(6-methyl-1,3-benzodioxol-5-ylmethylcarbonyl)thiophene; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-2-(6-methyl-1,3-benzodioxol-5-ylmethyl)thiophene; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-2-(6-methyl-1,3-benzodioxol-5-ylethyl)thiophene; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-N-(4-tolyl)thiophene-2-carboxamide; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-N-(4-methoxyphenyl)thiophene-2-carboxamide; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-N-(4-cyanophenyl)thiophene-2-carboxamide; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-N-(4-methoxycarbonylphenyl)thiophene-2-carboxamide; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-N-(4-chlorophenyl)thiophene-2-carboxamide; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-2-(6-methyl-1,3-benzodioxol-5-ylcarbonyl)thiophene; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-2-(6-methyl-1,3-benzodioxol-5-yloxy carbonyl)thiophene; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-2-(6-methyl-1,3-benzodioxol-5-ylvinyl)thiophene; 3-(2,1,3-benzothiadiazol-5-aminosulfonyl)-N-(6-acetyl-1,3-benzodioxol-5-ylcarbonyl)thiophene-2-carboxamide; and 3-([1,2,5]-thiadiazolo-[3,4-b]-pyridin-5-aminosulfonyl)-N-(6-methyl-1,3-benzodioxol-5-yl)thiophene-2-carboxamide.

z. European Patent Application Publication No. EP 768 304

In particular, compounds for use in the methods provided herein have the formula:

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- or pharmaceutically acceptable salts thereof, where R¹ is phenyl, substituted phenyl or heterocyclyl; R² is phenyl or substituted phenyl; R³ is hydroxy, lower alkoxy, or NR⁴R⁵; R⁴ is H or R⁶; R⁵ is H or -(CH₂)_mR⁶; or R⁴ and R⁵ together with the nitrogen atom to
- 15 which they are attached form a nitrogen-containing heterocyclic group; R⁶ is phenyl, substituted phenyl, cycloalkyl, heterocyclyl, lower alkyl, hydroxy-lower alkyl, amino-lower alkyl, carboxy-lower alkyl or lower alkoxy-carbonyl-lower alkyl; R^a is H, loweralkyl or hydroxy; R^b is H or lower alkyl; X is O or S; Y is O or S; Z is H, lower lkyl, aryl, aryl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl; m is 0, 1 or 2; and n is 0, 1 or 2.
- 20 Preferred compounds of this embodiment include 6-(4-tert-butylphenylsulfonylamino)-4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)pyrimidine-2-carboxylic acid; 4-(4-tert-butylphenylsulfonylamino)-5-(2-chloro-5-methoxyphenoxy)-6-(2-hydroxyethoxy)pyrimidine-2-carboxylic acid; 4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-6-(4-methoxyphenylsulfonylamino)pyrimidine-2-carboxylic acid; (RS)-
- 25 6-(4-tert-butylphenylsulfonylamino)-4-(2,3-dihydroxypropoxy)-5-(3-methoxyphenoxy)pyrimidine-2-carboxylic acid; 6-(4-tert-butylphenylsulfonylamino)-4-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)pyrimidine-2-carboxylic acid; N-phenyl 6-(4-tert-butylphenylsulfonylamino)-4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)pyrimidine-2-carboxamide; N-phenyl 4-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-6-(4-
- 30 methoxyphenylsulfonylamino)pyrimidine-2-carboxamide; N-phenyl 6-(4-tert-butylphenylsulfonylamino)-5-(2-methoxyphenoxy)-4-(2-hydroxyethoxy)pyrimidine-2-carboxamide; N-phenyl 4-(4-tert-butylphenylsulfonylamino)-5-(2-chloro-5-methoxyphenoxy)-6-(2-hydroxyethoxy)pyrimidine-2-carboxamide; N-(1H-tetrazol-5-yl)-4-(4-tert-butylphenylsulfonylamino)-6-(2-hydroxyethoxy)-5-(3-
- 35 methoxyphenoxy)pyrimidine-2-carboxamide; and 4-(2-hydroxyethoxy)-6-(5-isopropylpyridin-2-ylsulfonylamino)-5-(3-methoxyphenoxy)pyrimidine-2-carboxylic acid.

aa. U.S. Patent No. 6,043,265

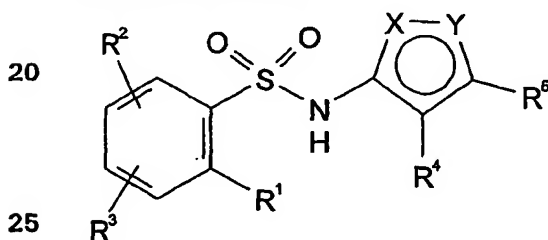
The compounds N-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-4-(2-

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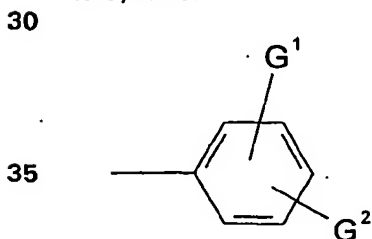
oxazolyl)[1,1'-biphenyl]-2-yl)methyl]-N,3,3-trimethylbutanamide, N-(4,5-dimethyl-3-isoxazolyl)-2'-formyl-N-[(2-methoxyethoxy)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, N-(4,5-dimethyl-3-isoxazolyl)-2'-formyl-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, N-(4,5-dimethyl-3-isoxazolyl)-2'-[(methylamino)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, N-(4,5-dimethyl-3-isoxazolyl)-2'-(hydroxymethyl)-N-[(2-methoxyethoxy)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, 2'-(bromomethyl)-N-(4,5-dimethyl-3-isoxazolyl)-N-[(2-methoxyethoxy)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-N-[(2-methoxyethoxy)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide, and 4-[[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl)methyl]amino]-2,2-dimethylbutanoic acid, and salts thereof, are intended for use in the methods provided herein.

15 **bb. U.S. Patent No. 6,080,774**

Certain of the compounds for use in the methods provided herein include those having the formula:



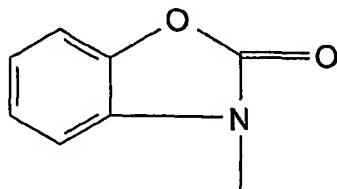
and pharmaceutically acceptable salts thereof, where one of X and Y is N and the other is O; R¹ is:



40 R² and R³ are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, or aralkoxy, any of which may be substituted with Z¹, Z² and Z³; (c) halo; (d) hydroxyl; (e)

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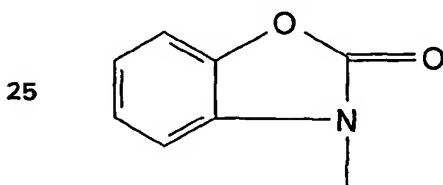
- cyano; (f) nitro; (g) $-C(O)H$ or $-C(O)R^6$; (h) $-CO_2H$ or CO_2R^6 ; (i) $-SH$, $-S(O)_nR^6$, $-S(O)_m-OH$, $-S(O)_m-OR^6$, $-O-S(O)_m-R^6$, $-O-S(O)_m-OH$, or $-O-S(O)_m-OR^6$; (j) $-Z^4-NR^7R^8$; or (k) $-Z^4-N(R^{11})-Z^5-NR^9R^{10}$; R^4 and R^5 are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, or aralkoxy, any of which may be substituted with Z^1 , Z^2 and Z^3 ; (c) halo; (d) hydroxyl; (e) cyano; (f) nitro; (g) $-C(O)H$ or $-C(O)R^6$; (h) $-CO_2H$ or CO_2R^6 ; (i) $-SH$, $-S(O)_nR^6$, $-S(O)_m-OH$, $-S(O)_m-OR^6$, $-O-S(O)_m-R^6$, $-O-S(O)_m-OH$, or $-O-S(O)_m-OR^6$; (j) $-Z^4-NR^7R^8$; or (k) $-Z^4-N(R^{11})-Z^5-NR^9R^{10}$; (l) R^4 and R^5 together are alkylene or alkenylene (either of which may be substituted with Z^1 , Z^2 and Z^3), completing a 4- to 8- membered saturated, unsaturated or aromatic ring together with the carbon atoms to which they are attached; R^6 is alkyl, alkenyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; R^7 , R^8 , R^9 , R^{10} and R^{11} are each independently (a) hydrogen; (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; R^7 and R^8 together may be alkylene or alkenylene (either of which may be substituted with Z^1 , Z^2 and Z^3), completing a 3- to 8- membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached; any two of R^9 , R^{10} and R^{11} together may be alkylene or alkenylene (either of which may be substituted with Z^1 , Z^2 and Z^3), completing a 3- to 8- membered saturated, unsaturated or aromatic ring together with the atoms to which they are attached; G^1 is (a) hydrogen; or (b) alkyl; G^2 is (a) hydroxyalkyl; (b) $-(CH_2)_mOR^6$; or (c) $-(CH_2)_m-NR^{12}R^{13}$; (d) mono-to-hexa-halo substituted alkyl (i.e., alkyl substituted with one, two, three, four, five or six halogen atoms); or (e) $-(CH_2)_nOR^{14}$; R^{12} and R^{13} are each independently (a) hydrogen; or (b) alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or aralkyl, any of which may be substituted with Z^1 , Z^2 and Z^3 ; or R^{12} and R^{13} together may be alkylene or alkenylene (either of which may be substituted with Z^1 , Z^2 and Z^3), completing a 3- to 8- membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached, or, together with the nitrogen atom to which they are attached form:



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- R^{14} is lower alkyl substituted with 1, 2 or 3 hlogen atoms; Z^1 , Z^2 and Z^3 are each independently (a) hydrogen; (b) halo; (c) hydroxy; (d) alkyl; (e) alkenyl; (f) aralkyl; (g) alkoxy; (h) aryloxy; (i) aralkoxy; (j) -SH, -S(O)_nZ⁶, -S(O)_m-OH, -S(O)_m-OZ⁶, -O-S(O)_m-Z⁶, -O-S(O)_mOH, or -O-S(O)_m-O-Z⁶; (k) oxo; (l) nitro; (m) cyano; (n) -C(O)H or -C(O)Z⁶; (o) -CO₂H or -CO₂Z⁶; (p) -Z⁴-NZ⁷Z⁸; (q) Z⁴-N(Z¹¹)-Z⁵-H; (r) Z⁴-N(Z¹¹)-Z⁵-Z⁶; or (s) -Z⁴-N(Z¹¹)-Z⁵-NZ⁷Z⁸; Z⁴ and Z⁵ are each independently (a) a single bond; (b) -Z⁹-S(O)_n-Z¹⁰-; (c) -Z⁹-C(O)-Z¹⁰-; (d) -Z⁹-C(S)-Z¹⁰-; (e) -Z⁹-O-Z¹⁰-; (f) -Z⁹-S-Z¹⁰-; (g) -Z⁹-O-C(O)-Z¹⁰-; or (h) -Z⁹-C(O)-O-Z¹⁰-; Z⁶ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl; Z⁷ and Z⁸ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, or Z⁷ and Z⁸ together are alkylene or alkenylene, completing a 3- to 8- membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached; Z⁹ and Z¹⁰ are each independently a single bond, alkylene, alkenylene, or alkynylene; Z¹¹ is (a) hydrogen; (b) alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, or aralkyl; or any two of Z⁷, Z⁸ and Z¹¹ together are alkylene or alkenylene, completing a 3- to 8- membered saturated, unsaturated, or aromatic ring together with the atoms to which they are attached; each m is independently 1 or 2; and each n is independently 0, 1, or 2.

- For this embodiment, it is preferred that R² and R³ are each independently hydrogen or alkyl; R⁴ and R⁵ are each independently alkyl; and R¹² and R¹³, together with the atoms to which they are attached, form:



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For this embodiment, most preferred compounds are those wherein R² and R³ are each hydrogen; and R⁴ and R⁵ are alkyl of 1 to 4 carbon atoms, especially methyl.

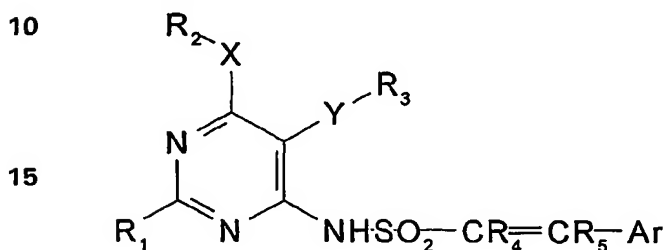
- Preferred compounds of this embodiment include N-(3,4-dimethyl-5-isoxazolyl)-2'-(hydroxymethyl)[1,1'-biphenyl]-2-sulfonamide; 4'-[(dimethylamino)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-4'-[(2-hydroxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-2'-(hydroxymethyl)-4'-(2-methylpropyl)[1,1'-biphenyl]-2-sulfonamide; 2'-(aminomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-methylpropyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-
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dimethyl-5-isoxazolyl)-4'-(1-hydroxy-2-methylpropyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-hydroxy-2-methylpropyl)[1,1'-biphenyl]-2-sulfonamide; N-(3,4-dimethyl-5-isoxazolyl)-4'-(3-hydroxy-2-methylpropyl)[1,1'-biphenyl]-2-sulfonamide; and N-(3,4-dimethyl-5-isoxazolyl)-2'-[(formylamino)methyl]-4'-(2-methylpropyl)[1,1'-biphenyl]-2-sulfonamide.

cc. U.S. Patent No. 6,083,955

Other compounds for use in the methods provided herein include those having the formula:



20 where Ar is an optionally substituted aryl group or optionally substituted five- to six-membered heteroaryl group; X is oxygen, sulfur or -NH-; Y is O or S; R₁ is hydrogen, optionally halogen-substituted lower alkyl, cycloalkyl, optionally substituted aryl or optionally substituted five- to six-membered heteroaryl; R₂ is lower alkyl lower alkenyl, lower alkynyl, and may be substituted with one to three substituent(s) selected from

25 hydroxyl, lower alkoxy, cycloalkyl halo, carboxyl and lower alkoxy carbonyl; R₃ is phenyl, which may be substituted with one to four substituent(s) selected from optionally halogen-substituted lower alkyl, lower alkoxy, halo, lower alkylthio, lower alkylsulfinyl, lower alkanesulfonyl, carboxyl, lower alkoxy carbonyl and carbamoyl; R₄ and R₅ are each independently hydrogen or lower alkyl.

30 Preferred compounds of this embodiment include:

N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-2-phenylethenesulfonamide; N-[6-methoxy-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-2-phenylethenesulfonamide; N-[6-(2-fluoroethoxy)-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-2-phenylethenesulfonamide; N-[6-(2-propynyloxy)-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-2-phenylethenesulfonamide; N-[6-methoxy-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-1-methyl-2-phenylethenesulfonamide; N-[6-methoxy-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-4-

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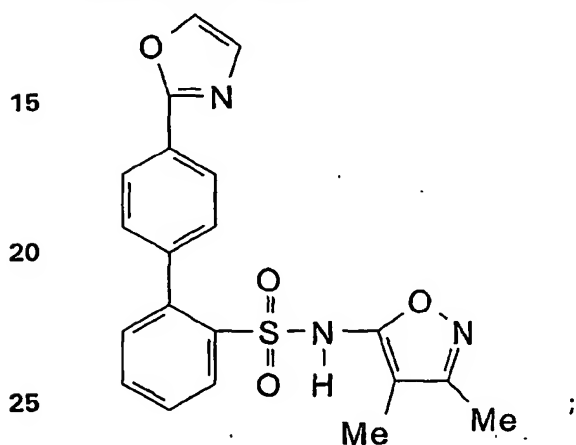
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pyrimidinyl]-1-ethyl-2-phenylethanesulfonamide; and N-[6-methoxy-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]-2-(2-thienyl)ethanesulfonamide.

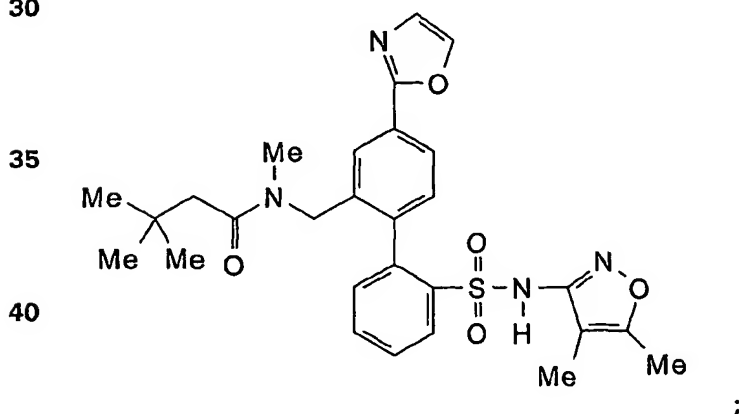
dd. Preferred compounds

Nonpeptide endothelin antagonists, especially sulfonamide endothelin
 5 antagonists (i.e., those containing a sulfonamide moiety $\text{-SO}_2\text{-NH-}$) are preferred, particularly those described in European Patent Application EP 702012; U.S. Patent Nos. 5,612,359 and 5,594,021; International Patent Application Publication Nos. WO 94/27979; WO 96/31492; WO 98/13366; and WO 98/49162. For example, among preferred compounds are the following compounds:

10 N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1, 1'-biphenyl]-2-sulfonamide, having the structure:

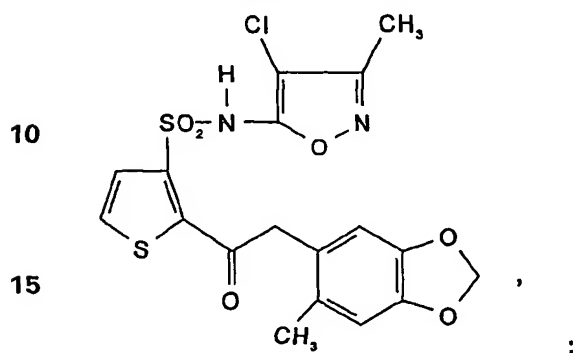


30 N-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino)sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl)methyl]-N,3,3-trimethylbutanamide, having the structure:

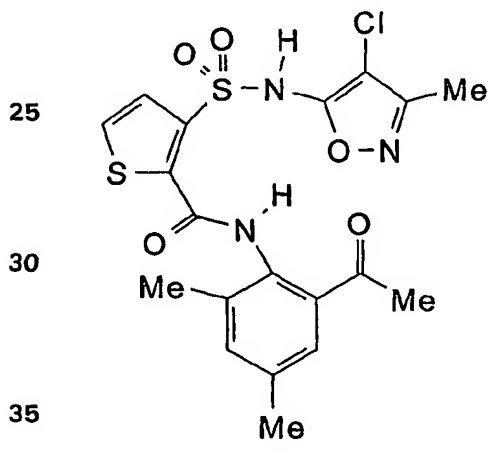


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N-(4-chloro-3-methyl-5-isoxazolyl)-2-[[3,4-(methylenedioxy)-6-methylphenyl]-acetyl]-thiophene-3-sulfonamide also designated 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide, having the structure:

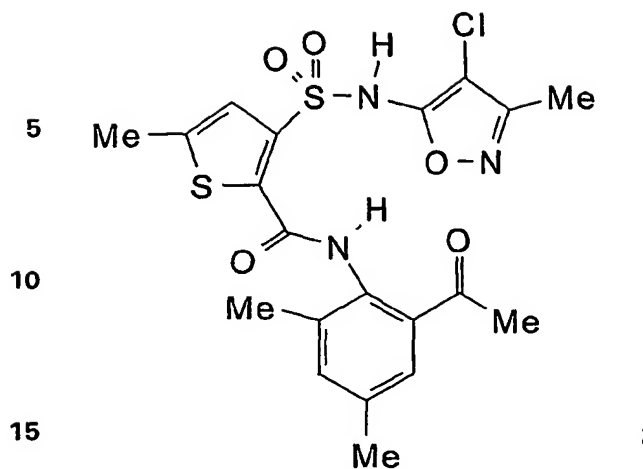


N-(2-acetyl-4,6-dimethylphenyl)3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide, having the structure:

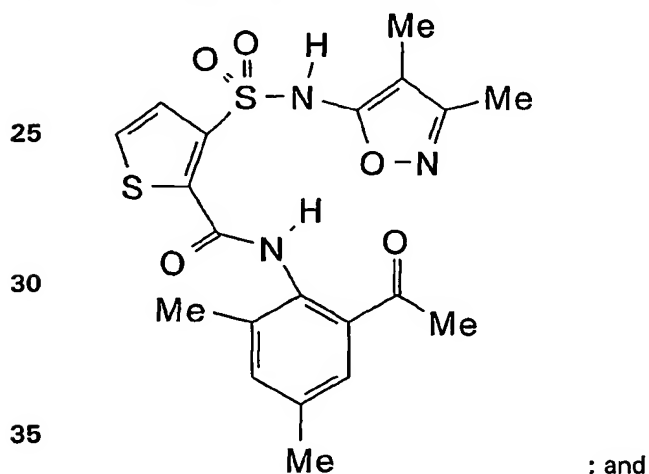


N-(2-acetyl-4,6-dimethylphenyl)3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide, having the structure:

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20 N-[2-acetyl-4,6-dimethylphenyl]-3-(((3,4-dimethyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide, having the structure:

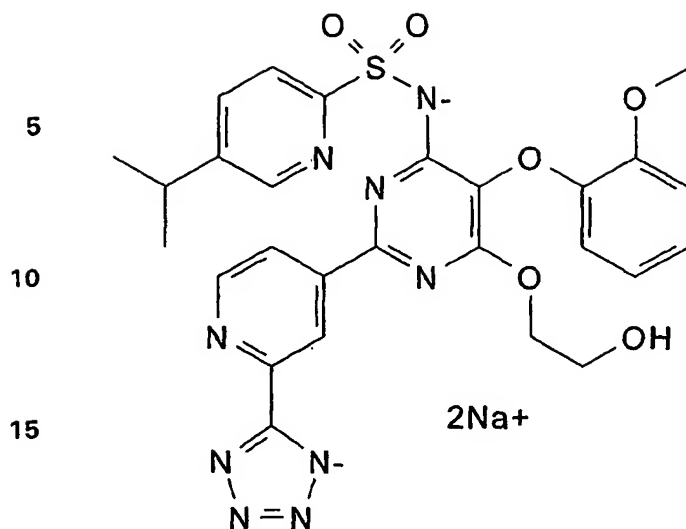


40 5-isopropyl-pyridine-2-sulfonic acid [6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(1H-tetrazol-5-yl)pyridin-4-yl]pyrimidin-4-yl]amide sodium salt (1:2) (also referred to as Ro61), having the structure:

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and pharmaceutically or veterinarily acceptable derivatives thereof.

Other compounds for use in the methods provided herein include BQ-123, (cyclo-(D-trp-D-asp-L-pro-D-val-L-leu)), BQ-153, BQ-238, BQ-485, BQ-610, BQ-788, BQ-928, TAK-044, FR139317 (perhydrozaepin-1-ylcarbonyl-L-leucyl-(1-methyl)-D-tryptophyl-[3-(2-pyridyl)]-D-alanine), RES-701-1, PD 142893 (acetyl-3,3-diphenyl-D-alanine)-L-leu-L-asp-L-ile-L-ile-L-trp), PD 145065, CP 170687, Ac-DBhg16-leu-asp-ile, ET-1[Dprl-asp 15], Ro 61-0612, To 61-1790, To 42-2005, Ro 46-2005, Ro 46-8443, Ro 47-0203 (also known as bosentan), PD 155080, PD 156707, SB 209670, SB 217242, L-744,453, L-749,329, L-754,142, CGS 27830, BMS 182874, LU 135252, S-1039, mA386, A-127722, Nz-arg-3-(isoxazolylsulfamoyl)-2-thiophenecarboxamide and EQ 123.

6. Combination Therapy

In the methods provided herein, the endothelin antagonist may, for example, be employed alone, in combination with one or more other endothelin antagonists, or with another compound useful for the prevention or treatment of endothelin-mediated disorders, such as a poly- β -1 \rightarrow 4-N-acetylglucosamine (p-GlcNAc) polysaccharide matrix; angiotensin converting enzyme (ACE) inhibitors such as captopril; dopamine receptor agonists such as apomorphine; renin inhibitors; angiotensin II (All) antagonists such as irbesartan ((2-n-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one); dual NEP-ACE inhibitors such as [4S-[4 α (R*), 7 α , 10 α]]-octahydro-4-(2-mercapto-1-oxo-3-phenylpropyl)amino]-5-oxo-7H-pyrido[2,1-b][1,3]thiazepine-7-

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carboxylic acid (BMS-186716, U.S. Patent No. 5,508,272), [S-(R*,R*)]-hexahydro-6-
 [(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid
 (BMS-189921, U.S. Patent No. 5,552,397), alatriopril, sampatrilat, MDL 100240, and
 CGS 30440; PDE V inhibitors such as sildenafil (see Terrett et al., *Bioorg. Med. Chem.*

- 5 *Ltrs.*, 6:1819-1824 (1996)), GF 196960 and IC-351; alpha adrenergic blockers such as
 phentolamine; vasoactive intestinal peptide (VIP); nitric oxide synthase substrates such
 as L-arginine; nitric oxide donors such as sodium nitroprusside, nitroglycerin, glyceryl
 trinitrate, SIN-1, isosorbidmononitrate or isosorbiddinitrate; and prostaglandin E₁ acting
 compounds such as alprostadiol. Such other pharmaceutically or veterinarily active
 10 agents may be administered prior to, during or together with, or following administration
 of the endothelin antagonist. If formulated as a fixed dose, such combination products
 preferably employ the endothelin antagonists within the dosage range described above
 and the other pharmaceutically or veterinarily active agent within its approved dosage
 range.

15 **7. Pharmaceutically or veterinarily acceptable derivatives of the compounds**

- Also of interest are any pharmaceutically or veterinarily acceptable derivatives,
 including salts, esters, acids and bases, solvates, hydrates and prodrugs of the sulfona-
 mides. Preferred are pharmaceutically or veterinarily-acceptable salts, including, but not
 limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine,
 20 chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines,
 ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-
 chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines,
 piperazine, tris(hydroxymethyl)aminomethane, alkali metal salts, such as but not limited
 to lithium, potassium and sodium, alkali earth metal salts, such as but not limited to
 25 barium, calcium and magnesium, transition metal salts, such as but not limited to zinc
 and other metal salts, such as but not limited to sodium hydrogen phosphate and
 disodium phosphate, preferably sodium salts, more preferably the sodium salt, and also
 including, but not limited to, salts of mineral acids, such as but not limited to
 hydrochlorides and sulfates, salts of organic acids, such as but not limited to acetates,
 30 lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and
 fumarates. Alkali metal salts, particularly sodium salts, are preferred herein. Most
 preferred salts are sodium salts.

Of interest are formulations of pharmaceutically or veterinarily acceptable
 derivatives, including salts, esters, acids and bases, solvates, hydrates and prodrugs of

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the sulfonamides. In particular, derivatives of neutral sulfonamide compounds that yield formulations of greater stability than formulations containing the corresponding neutral compounds are provided. Preferred are salts, particularly alkali metal salts, and more preferably sodium salts, including salts prepared from sodium compounds, including, but
5 not limited to, sodium bicarbonate in which the resulting product is a sodium salt and disodium hydrogen phosphate in which the resulting compound is a sodium hydrogen phosphate salt. The sodium salt of each compound is most preferred.

The formulations are compositions suitable for administration by any desired route and include solutions, suspensions, emulsions, tablets, dispersible tablets, pills,
10 capsules, powders, dry powders for inhalers, sustained release formulations, aerosols for nasal and respiratory delivery, patches for transdermal delivery and any other suitable route. The compositions should be suitable for oral administration, parenteral administration by injection, including subcutaneously, intramuscularly or intravenously as an injectable aqueous or oily solution or emulsion, transdermal administration and
15 other selected routes.

The formulations provided herein are for administration by a selected route and contain effective concentrations of pharmaceutically or veterinarily-acceptable salts of the above-noted compounds. The formulations deliver amounts effective for the treatment of laminitis, particularly equine or bovine laminitis, more particularly equine
20 laminitis.

D. Preparation of the compounds

The preparation of the neutral (*i.e.*, free) sulfonamide compounds that possess the requisite activities are set forth in U.S. Patent Nos. 5,464,853, 5,594,021, 5,591,761, 5,571,821, 5,514,691, 5,464,853, commonly owned copending U.S.
25 application Serial Nos. 08/721,183 and 08/847,797, and commonly owned published International PCT application Nos. WO 96/31492 and WO 97/27979. Representative syntheses are set forth the Examples. Compounds whose synthesis is not explicitly exemplified herein or in the above-listed patents and published International PCT applications can be synthesized by routine modification of one or more methods
30 described in detail in the Examples by substituting appropriate readily available reagents.

Salts, acids and other derivatives thereof can be synthesized as outlined and exemplified herein, or by other methods known to those of skill in the art.

1. Neutral compounds

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In general, most of the syntheses involve the condensation of a sulfonyl chloride with an aminoisoxazole in dry pyridine or in tetrahydrofuran (THF) and sodium hydride. The sulfonyl chlorides and aminoisoxazoles either can be obtained commercially or synthesized according to methods described in the Examples or using
5 other methods available to those of skill in this art (see, e.g., U.S. Patent Nos. 4,659,369, 4,861,366 and 4,753,672).

The N-(alkylisoxazolyl)sulfonamides can be prepared by condensing an aminoisoxazole with a sulfonyl chloride in dry pyridine with or without the catalyst 4-(dimethylamino)pyridine. The N-(3,4-dimethyl-5-isoxazolyl)sulfonamides and N-(4,5-
10 dimethyl-3-isoxazolyl)sulfonamides can be prepared from the corresponding aminodimethylisoxazole, such as 5-amino-3,4-dimethylisoxazole. For example, N-(3,4-dimethyl-5-isoxazolyl)-2-(carbomethoxy)thiophene-3-sulfonamide was prepared from 2-methoxycarbonylthiophene-3-sulfonyl chloride and 5-amino-3,4-dimethylisoxazole in dry pyridine.

15 The N-(4-haloisoxazolyl)sulfonamides can be prepared by condensation of amino-4-haloisoxazole with a sulfonyl chloride in THF with sodium hydride as a base. For example, N-(4-bromo-3-methyl-5-isoxazolyl)thiophene-2-sulfonamide was prepared from 5-amino-4-bromo-3-methylisoxazole and thiophene-2-sulfonyl chloride in THF and sodium hydride. N-(4-bromo-3-methyl-5-isoxazolyl)-5-(3-isoxazolyl)thiophene-2-sulfona-
20 mide was prepared from 5-amino-4-bromo-3-methylisoxazole and 5-(3-isoxazolyl)thiophene-2-sulfonyl chloride.

Alternatively, compounds, such as those in which Ar² is thienyl, furyl and pyrrolyl herein, may be prepared by reacting an appropriate sulfonyl chloride with a 5-aminoisoxazole substituted at the 3 and 4 positions, such as 5-amino-4-bromo-3-
25 methylisoxazole, in tetrahydrofuran (THF) solution containing a base, such as sodium hydride. Following the reaction, the THF is removed under reduced pressure, the residue dissolved in water, acidified and extracted with methylene chloride. The organic layer is washed and then dried over anhydrous magnesium sulfate, the solvents are evaporated and the residue is purified by recrystallization using hexanes/ethyl acetate to
30 yield pure product.

These sulfonamides also can be prepared from the corresponding sulfonyl chloride and the aminoisoxazole in pyridine with or without a catalytic amount of 4-dimethylaminopyridine (DMAP). In some cases, the bis-sulfonyl compound is obtained as the major or exclusive product. The bis-sulfonated products can be readily

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hydrolyzed to the sulfonamide using aqueous sodium hydroxide and a suitable co-solvent, such as methanol or tetrahydrofuran, generally at room temperature.

Other examples include:

- (a) N-(4-bromo-3-methyl-5-isoxazolyl)-2-(N-phenylamino-carbonyl)thiophene-3-sulfonamide was prepared from N-(4-bromo-3-methyl-5-isoxazolyl)-2-carboxylthiophene-3-sulfonamide, aniline and 1-ethyl-3'-[3-dimethylaminopropyl]-carbodiimide (EDCI). N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(4-methoxyphenyl)aminocarbonyl]thiophene-3-sulfonamide was prepared from 4-methoxyaniline, N,N'-diisopropylethylamine and N-(4-bromo-3-methyl-5-isoxazolyl)-2-carboxylthiophene-3-sulfonamide. N-(4-bromo-3-methyl-5-isoxazolyl)-2-(benzylaminocarbonyl)thiophene-3-sulfonamide was prepared from N-(4-bromo-3-methyl-5-isoxazolyl)-2-carboxylthiophene-3-sulfonamide and benzylamine as described above.

- N-(4-bromo-3-methyl-5-isoxazolyl)-2-carboxylthiophene-3-sulfonamide was prepared from N-(4-bromo-3-methyl-5-isoxazolyl)-2-(carbomethoxy)thiophene-3-sulfonamide, which was prepared from the condensation of 5-amino-4-bromo-3-methylisoxazole and 2-(carbomethoxy)thiophene-3-sulfonyl chloride.

- (b) N-(4-bromo-3-methyl-5-isoxazolyl)-1-(4'-isopropylphenyl)pyrrole-2-sulfonamide and N-(4-bromo-3-methyl-5-isoxazolyl)-1-(4'-isopropylphenyl)pyrrole-3-sulfonamide were prepared from 5-amino-4-bromo-3-methylisoxazole and a mixture of 1-(4'-isopropylphenyl)pyrrole-2-sulfonyl chloride and 1-(4'-isopropylphenyl)pyrrole-3-sulfonyl chloride. These sulfonyl chlorides were prepared from 1-(4'-isopropylphenyl)pyrrole-2-sulfonic acid, phosphorus oxychloride and phosphorus pentachloride. 1-(4'-isopropylphenyl)pyrrole-2-sulfonic acid was prepared from 1-(4'-isopropylphenyl)pyrrole and chlorosulfonic acid. 1-(4'-isopropylphenyl)pyrrole was prepared from 4-isopropylaniline and 2,5-dimethoxytetrahydrofuran.

2. Salts of the neutral compounds

- Pharmaceutically or veterinarily-acceptable salts of the compounds may be prepared by the exemplified method or any other method known to those of skill in the art. As exemplified herein, in the case of organic salts, the organic base, such as N,N'-dibenzylethylenediamine, chlorprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine, or tris(hydroxymethyl)aminomethane, may be mixed with an equimolar amount of the sulfonamide. Subsequent recovery of

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the salt by crystallization, precipitation, concentration of the solution, lyophilization, spray-drying, chromatography, including, but not limited to, normal- and reverse-phase chromatography or resin chromatography, or any other method known to those of skill in the art would provide the desired salts. The pharmaceutically or veterinarily

5 acceptable cationic salts can be prepared by reacting the acid forms with an appropriate base.

Sodium salts, and other metal salts, of the compounds may be prepared by the method set forth in U.S. Patent No. 5,783,705. Briefly, a solution of the sulfonamide in an organic solvent, such as ethyl acetate, is washed with several portions (i.e., 5 or
10 more) of a saturated solution of sodium bicarbonate or sodium carbonate, preferably sodium bicarbonate. Concentration of the organic solution provided the sodium salts of the sulfonamides. The sulfonamide sodium salts can be further purified, if required, by crystallization from an appropriate solvent, such as, for example, dichloromethane/diethyl ether. Further purification may optionally be performed by filtering an aqueous
15 solution of the sulfonamide sodium salts to remove particulates, liberating the free sulfonamides by acidification with aqueous hydrochloric acid (e.g., 4 N), and repeating the ethyl acetate/aqueous sodium bicarbonate procedure. Crystallization of the sulfonamide salts from the solvent, such as dichloromethane/diethyl ether or ethanol/methyl tert-butyl ether, provides sulfonamide sodium salts of greater than 98% purity.

20 3. Other derivatives

Prodrugs and other derivatives of the compounds suitable for administration to humans may also be designed and prepared by methods known to those of skill in the art (see, e.g., Nogrady (1985) Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392).

25 Compounds described herein have been synthesized and tested for activity in in vitro assays and, in some cases, in in vivo animal models. Nuclear magnetic resonance spectroscopic (NMR), mass spectrometric, infrared spectroscopic and high performance liquid chromatographic analyses indicated that the synthesized compounds have structures consistent with those expected for such compounds and are generally at
30 least about 98% pure. All of the compounds exemplified or described herein exhibited activity as endothelin antagonists.

E. Evaluation of the bioactivity of the compounds

Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess any biological

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activities of an endothelin peptide or the ability to interfere with or inhibit endothelin peptides. Compounds that exhibit in vitro activities, such as the ability to bind to endothelin receptors or to compete with one or more of the endothelin peptides for binding to endothelin receptors can be used in the methods for isolation of endothelin
5 receptors and the methods for distinguishing the specificities of endothelin receptors, and are candidates for use in the methods of treating endothelin-mediated disorders.

Thus, other preferred compounds of formulae I-XXVII, in addition to those specifically identified herein, that are endothelin antagonists or agonists may be identified using such screening assays.

10 **Identifying compounds that modulate the activity of an endothelin peptide**

The compounds are tested for the ability to modulate the activity of endothelin-1. Numerous assays are known to those of skill in the art for evaluating the ability of compounds to modulate the activity of endothelin (see, e.g., U.S. Patent No.
15 5,114,918 to Ishikawa et al.; EP A1 0 436 189 to BANYU PHARMACEUTICAL CO., LTD. (October 7, 1991); Borges et al. (1989) Eur. J. Pharm. 165: 223-230; Filep et al. (1991) Biochem. Biophys. Res. Commun. 177: 171-176). In vitro studies may be corroborated with in vivo studies (see, e.g., U.S. Patent No. 5,114,918 to Ishikawa et al.; EP A1 0 436 189 to BANYU PHARMACEUTICAL CO., LTD. (October 7, 1991)) and
20 pharmaceutical or veterinary activity thereby evaluated. Such assays are described in the Examples herein and include the ability to compete for binding to ET_A and ET_B receptors present on membranes isolated from cell lines that have been genetically engineered to express either ET_A or ET_B receptors on their cell surfaces.

The properties of a potential antagonist may be assessed as a function of its
25 ability to inhibit an endothelin induced activity in vitro using a particular tissue, such as rat portal vein and aorta as well as rat uterus, trachea and vas deferens (see e.g., Borges, R., Von Grafenstein, H. and Knight, D.E., "Tissue selectivity of endothelin," Eur. J. Pharmacol 165:223-230, (1989)). The ability to act as an endothelin antagonist in vivo can be tested in hypertensive rats, ddy mice or other recognized animal models
30 (see, Kaltenbronn et al. (1990) J. Med. Chem. 33:838-845, see, also, U.S. Patent No. 5,114,918 to Ishikawa et al.; and EP A1 0 436 189 to BANYU PHARMACEUTICAL CO., LTD (October 7, 1991); see, also Bolger et al. (1983) J. Pharmacol. Exp. Ther. 225:291-309). Using the results of such animal studies, pharmaceutical or veterinary effectiveness may be evaluated and pharmaceutically or veterinarily effective dosages

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determined. A potential agonist may also be evaluated using in vitro and in vivo assays known to those of skill in the art.

Endothelin activity can be identified by the ability of a test compound to stimulate constriction of isolated rat thoracic aorta (Borges et al. (1989) "Tissue selectivity of endothelin" Eur. J. Pharmacol. 165: 223-230). To perform the assay, the endothelium is abraded and ring segments mounted under tension in a tissue bath and treated with endothelin in the presence of the test compound. Changes in endothelin induced tension are recorded. Dose response curves may be generated and used to provide information regarding the relative inhibitory potency of the test compound.

Other tissues, including heart, skeletal muscle, kidney, uterus, trachea and vas deferens, may be used for evaluating the effects of a particular test compound on tissue contraction.

Endothelin isotype specific antagonists may be identified by the ability of a test compound to interfere with endothelin binding to different tissues or cells expressing different endothelin-receptor subtypes, or to interfere with the biological effects of endothelin or an endothelin isotype (Takayanagi et al. (1991) Reg. Pep. 32: 23-37, Panek et al. (1992) Biochem. Biophys. Res. Commun. 183: 566-571). For example, ET_B receptors are expressed in vascular endothelial cells, possibly mediating the release of prostacyclin and endothelium-derived relaxing factor (De Nucci et al. (1988) Proc. Natl. Acad. Sci. USA 85:9797). ET_A receptors are not detected in cultured endothelial cells, which express ET_B receptors.

The binding of compounds or inhibition of binding of endothelin to ET_B receptors can be assessed by measuring the inhibition of endothelin-1-mediated release of prostacyclin, as measured by its major stable metabolite, 6-keto PGF_{1 α} , from cultured bovine aortic endothelial cells (see, e.g., Filep et al. (1991) Biochem. and Biophys Res. Commun. 177: 171-176). Thus, the relative affinity of the compounds for different endothelin receptors may be evaluated by determining the inhibitory dose response curves using tissues that differ in receptor subtype.

Using such assays, the relative affinities of the compounds for ET_A receptors and ET_B receptors have been and can be assessed. Those that possess the desired properties, such as specific inhibition of binding of endothelin-1, are selected. The selected compounds that exhibit desirable activities may be therapeutically useful and are tested for such uses using the above-described assays from which in vivo effectiveness may be evaluated (see, e.g., U.S. Patent No. 5,248,807; U.S. Patent No.

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5,240,910; U.S. Patent No. 5,198,548; U.S. Patent No. 5,187,195; U.S. Patent No. 5,082,838; U.S. Patent No. 5,230,999; published Canadian Application Nos. 2,067,288 and 2071193; published Great Britain Application No. 2,259,450; Published International PCT Application No. WO 93/08799; Benigi *et al.* (1993) *Kidney*

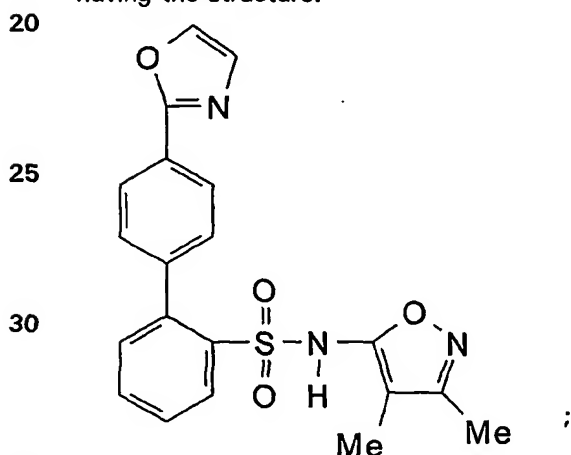
- 5 *International* 44:440-444; and Nirei *et al.* (1993) *Life Sciences* 52:1869-1874). Compounds that exhibit *in vitro* activities that correlate with *in vivo* effectiveness will then be formulated in suitable pharmaceutical or veterinary compositions and used as therapeutics.

F. Methods of Use

- 10 Methods of use of endothelin antagonists are provided. Any endothelin antagonist is contemplated for use in the methods provided herein. Preferred endothelin antagonists are those described in detail herein. More preferred endothelin antagonists for use in the methods provided herein include sulfonamides disclosed in European Patent Application EP 702012; U.S. Patent Nos. 5,612,359 and 5,594,021;
- 15 International Patent Application Publication Nos. WO 94/27979; WO 96/31492; WO 98/13366; and WO 98/49162. For example, among preferred endothelin antagonists are:

N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1, 1'-biphenyl]-2-sulfonamide,

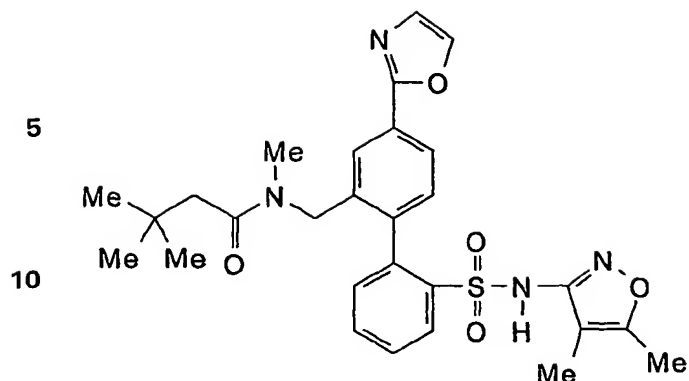
having the structure:



N-[[2'-[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide, having the structure:

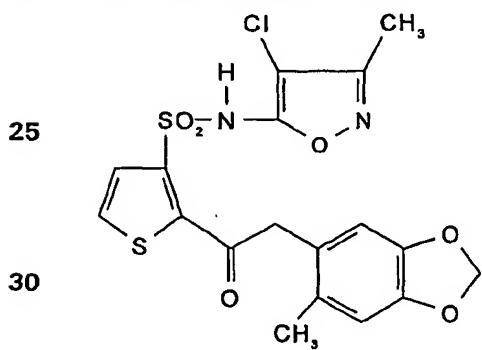
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N-(4-chloro-3-methyl-5-isoxazolyl)-2-([3,4-(methylenedioxy)-6-methylphenyl]-acetyl)-thiophene-3-sulfonamide also designated 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide, having the structure:



N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide, having the structure:

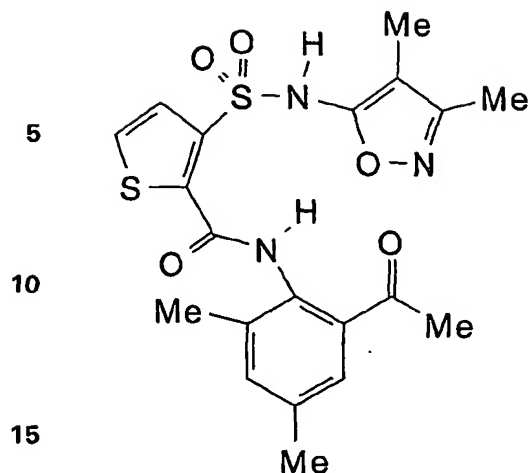
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Cc1cc(Cl)c(NC(=O)c2cc3cc(C)c(C)cc3c2C(=O)Nc2cc3cc(C)c(C)cc3c2C(=O)c2ccsc2)cc1Cc1cc(Cl)c(NC(=O)c2cc(C)c(C)cc2C(=O)c3cc(C)scc3S(=O)(=O)N1)c(O1)c1

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and pharmaceutically or veterinarily acceptable derivatives thereof. The endothelin
20 antagonists are useful for treating, preventing, or ameliorating one or more symptoms of
disorders that are caused by endothelin activity or disorders in which endothelin activity
is otherwise implicated. Such endothelin-mediated disorders include, but are not limited
to, menopause; osteoporosis and metabolic bone disorders; climacteric disorders
including hot flushes or flashes, abnormal clotting patterns, urogenital discomfort and
25 increased incidence of cardiovascular disease, and other disorders associated with the
reduction in ovarian function in middle-aged women; pre-eclampsia; and control and
management of labor during pregnancy.

Preferably, a medicament containing the compound is administered intravenously
(IV), although treatment by local or topical administration may be tolerated in some
30 instances. Generally, the medicament containing the compound is injected into the
circulatory system of a subject in order to deliver a dose to the targeted cells. Targeting
may be effected by linking the compound to a targeting agent specific for endothelin
receptors, particularly endothelin-1 receptors. Dosages may be determined empirically,
but will typically be in the range of about 0.01 mg to about 100 mg of the compound
35 per kilogram of body weight as a daily dosage.

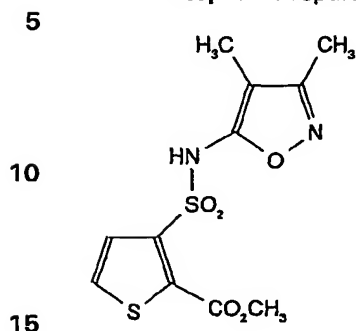
The following examples are included for illustrative purposes only and are not
intended to limit the scope of the invention.

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EXAMPLE 1

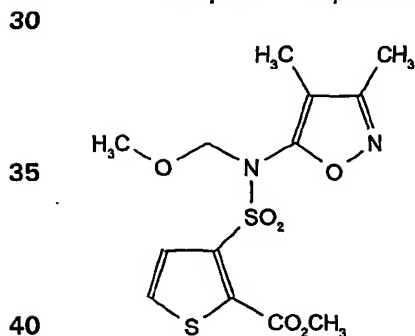
Preparation of compound 7: N-(2-acetyl-4,6-dimethylphenyl)-3-[(3,4 dimethyl-5-isoxazolyl)amino]sulfonyl}-2-thiophenecarboxamide

Step 1: Preparation of compound 1:



To a 250 mL round-bottom flask equipped with a magnetic stir bar was added 20.0 gm of 5-amino-3,4-dimethylisoxazole, 50 mL of pyridine, and 2.0 gm (catalytic amount) of dimethylaminopyridine. The mixture was cooled in an ice bath as 21.5 gm of 2-carboxymethyl-3-thiophenesulfonyl chloride was added in portions. The flask was sealed, the ice bath removed, and the reaction stirred at room temperature overnight. The majority of the pyridine was removed by rotary evaporation and the residual materials partitioned between ethyl acetate and 2N HCl. The layers were separated and the aqueous layer extracted with ethyl acetate (2X). The combined extracts were washed with dilute HCL (2X), brine (2X), and then dried over magnesium sulfate. Filtration and condensation by rotary evaporation yielded 23.2 gm of compound 1 as an oil.

Step 2A: Preparation of compound 2.

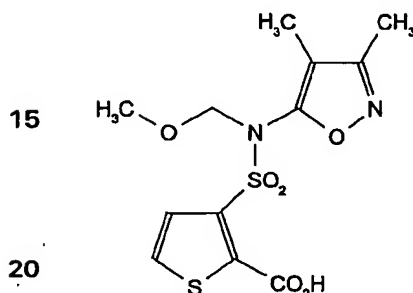


To a 1L round-bottom flask equipped with a magnetic stir bar and dropping funnel was added 23.1 gm of compound 1, 500 mL of methylene chloride, and 28.4 gm

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of diisopropylamine. The reaction was cooled in an ice bath and 6.0 mL of bromomethylmethyl ether was added dropwise. The ice bath was removed and the reaction stirred at room temperature overnight. At this point, 200 mL of water was added and the reaction stirred for 30 min. The layers were separated and the aqueous layer extracted (2X) with methylene chloride. The combined organic layers were then washed with 0.5 N HCl, water, saturated sodium bicarbonate, brine, and finally dried over magnesium sulfate. Filtration and rotary evaporation yielded an oil which was further purified by silica gel chromatography using 25 - 30% ethyl acetate/hexane as the eluant to afford 21.5 gm of compound 2 as an oil.

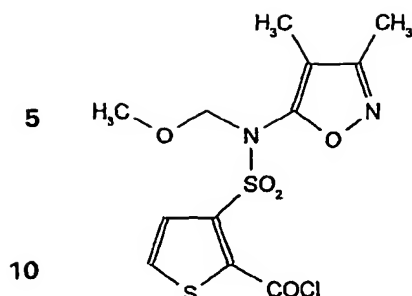
Step 2B: Preparation of compound 3.



To a 500 mL round bottom flask equipped with a magnetic stir bar was added 21.4 gm of compound 2, 120 mL of tetrahydrofuran, and 120 mL of 1N sodium hydroxide. The reaction was rapidly stirred until complete reaction (approximately 3 - 4 hr). The majority of the tetrahydrofuran was removed by rotary evaporation and the residual materials mixed with 50 mL of water. This mixture was then acidified by the addition of 130 mL of 1N HCl and then extracted with 200 mL (2X) of ethyl acetate. The combined extracts were washed with water (50 mL), then brine (50mL), and finally dried with magnesium sulfate. Filtration and condensation by rotary evaporation yielded 20.1 gm of compound 3 as a yellow oil which solidified upon standing.

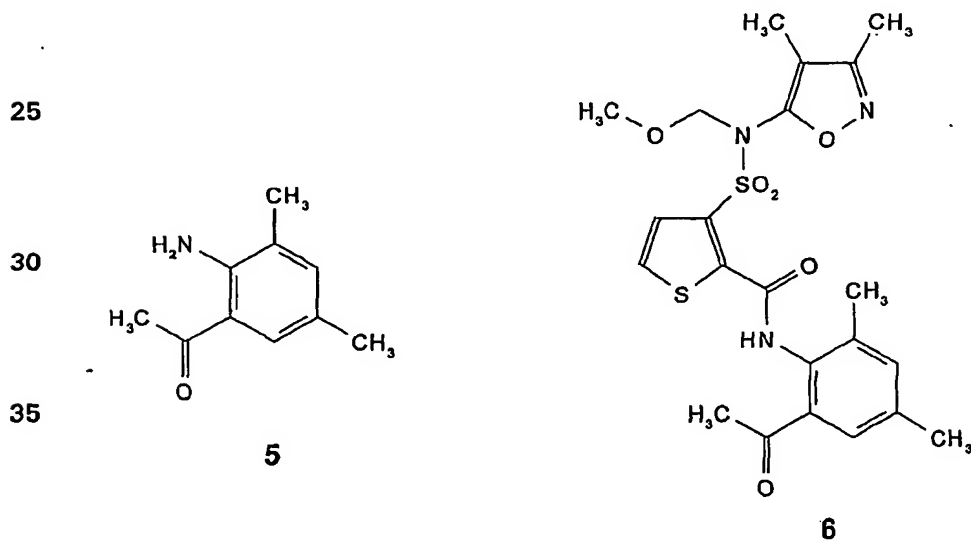
Step 2C: Preparation of compound 4.

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To a 1 L round bottom flask equipped with a magnetic stir bar and dropping funnel was added 19.7 gm of compound 3, 200 mL of methylene chloride, and 5 drops of pyridine. A solution of 128 mL of oxalyl chloride in 100 mL of methylene chloride was added dropwise. The dropping funnel was then replaced with a reflux condenser and the reaction heated to gentle reflux for 3 hr. after which it was condensed by rotary evaporation to yield 20.9 gm of compound 4 as a brown solid. This material was used directly in Step 3 without further purification.

Step 3: Preparation of compound 6.

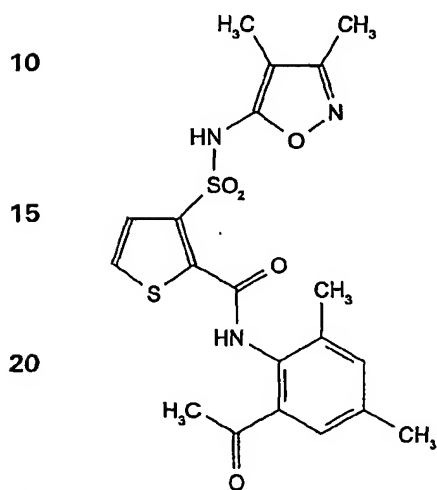


To a 1-L round bottom flask equipped with a magnetic stir bar and dropping funnel was added 18.5 gm of 2-acetyl-4,6-dimethylaniline (5) and 150 mL of methylene chloride. To this was added dropwise a solution of 20.7 gm of compound 4 dissolved in 350 mL of methylene chloride. The reaction was stirred at room temperature for 3 hr. and then condensed by rotary evaporation. To the residual materials was added 200

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mL of ether and the mixture was filtered. The filter cake was washed with 3X 100 mL of ether. The combined filtrates were washed with 3X 100mL of 1N HCl followed by 100 mL each with water, sat. sodium bicarbonate, and brine. The solution was then dried with magnesium sulfate, filtered, and condensed by rotary evaporation to yield a semi-crystalline material. This material was triturated with 200 mL of ether to yield 23.7 gm of compound 6 as a white solid.

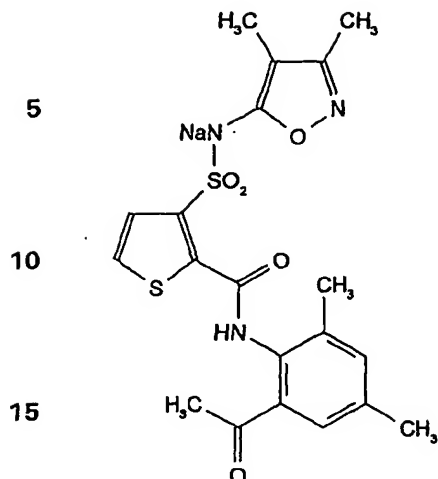
Step 4A: Preparation of compound 7.



To a 500 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser was added 23.7 gm of compound 6, 180 mL of methanol, and 90 mL of conc. HCl. The mixture was heated to reflux for 4 hr. Heating was discontinued and the mixture stirred and cooled with an ice bath. After approximately 30 min. the mixture was filtered and the filter cake washed with a mixture of water and methanol to yield 18.3 gm of compound 7. This material was recrystallized from ethyl acetate/hexane to give 16.8 gm of material as a white solid: mp 158 - 160 °C.

Step 4B: Preparation of compound 7 sodium salt.

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20 To 16.8 gm of compound 7 solubilized in 800 mL of ethyl acetate and 200 mL of tetrahydrofuran was added 100 mL of saturated sodium bicarbonate. The layers were separated and the organic layer washed with an additional 2X 100 mL of sat. sodium bicarbonate. The combined bicarbonate washes were back extracted with ethyl acetate and the combined organic solutions dried over magnesium sulfate, filtered, and

25 condensed by rotary evaporation to yield a foam. This material was solubilized in 300 mL of water and the resulting solution filtered and lyophilized to yield 15.5 gm of compound 7 sodium salt as a white solid.

EXAMPLE 2

30 Preparation of compound 9: N-(2-cyano-3,4,6-trimethylphenyl)-3-[[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-2-thiophenecarboxamide

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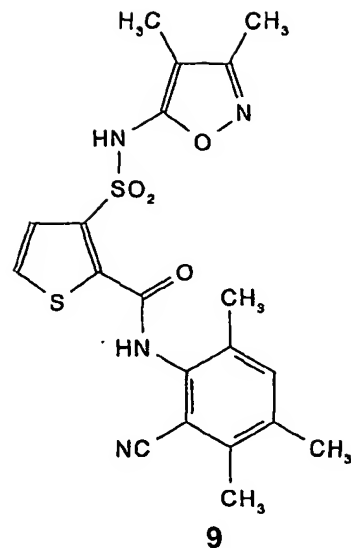
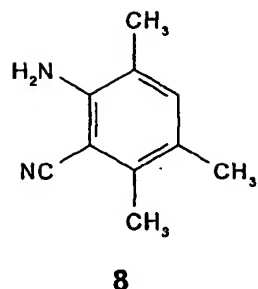
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N-(2-cyano-3,4,6-trimethylphenyl)-3-([(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl)-2-thiophenecarboxamide, was prepared by the procedure of Example 1 except that 2-cyano-3,4,6-trimethylaniline (**8**) was substituted for 2-acetyl-4,6-dimethylaniline in Step 3.

EXAMPLE 3

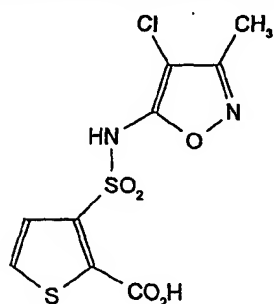
Preparation of compound 16: 3-([(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl)-N-(3,4,6-trimethyl-2-propanoylphenyl)-2-thiophenecarboxamide

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Step 1: Preparation of compound 10: 3-([(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl)-2-thiophenecarboxylic acid

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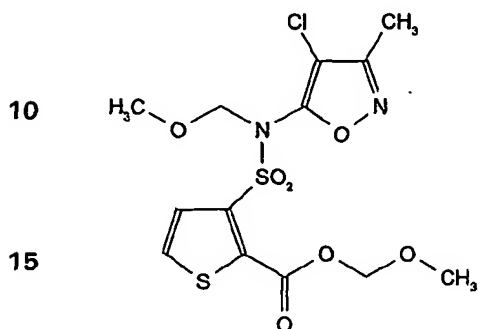
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To a 500 mL round bottom flask containing 46.5 g of 3-([(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl)-2-thiophenecarboxylic acid methyl ester was added 250 mL of 1 N sodium hydroxide. The mixture was stirred until no starting material remained. The reaction solution was acidified with 2 N hydrochloric acid, ethyl acetate extracted

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(3 x 100 mL). The combined extracts were dried (MgSO₄), filtered and condensed by rotary evaporation to yield 42.5 g of compound 10 as a solid.

Step 2A: Preparation of compound 11: 3{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-methoxymethyl-2-thiophenecarboxylic acid methoxymethyl ester.

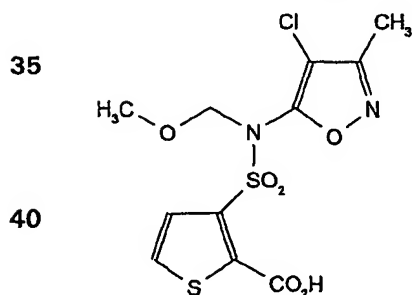


20 To a 2-L round bottom flask equipped with a magnetic stir bar and dropping funnel was added 42.5 gm of compound 10, 500 mL of methylene chloride, and 40.1 gm of diisopropylethylamine. The reaction mixture was cooled with an ice bath and 21.5 mL of bromomethylmethyl ether was added dropwise. The ice bath was removed and the reaction stirred at room temperature overnight. 200 mL of water was added

25 and the reaction mixture stirred for 30 min. The layers were separated and the aqueous layer washed with 100 mL of methylene chloride. The combined organic layers were washed with 50 mL each of 0.5 N HCl, water, sat. sodium bicarbonate, brine and then finally dried with magnesium sulfate. The mixture was filtered and the filtrate condensed by rotary evaporation to yield an oil that was further purified by silica gel

30 chromatography using 25 - 30% ethyl acetate/hexane as the eluant to yield 38.1 gm of compound 11 as an oil.

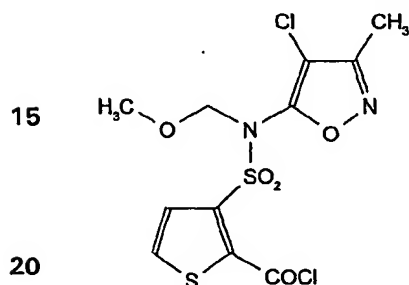
Step 2B: Preparation of compound 12.



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To a 1-L round bottom flask equipped with a magnetic stir bar was added 38 gm of compound 11, 250 mL of tetrahydrofuran, and 250 mL of 1N sodium hydroxide. The reaction was rapidly stirred until complete reaction (approximately 4 hr). The majority of the tetrahydrofuran was removed by rotary evaporation and the residual materials were mixed with 50 mL of water. This solution was then acidified by the addition of 260 mL of 1N HCl. This mixture was then twice extracted with 200 mL of ethyl acetate. The combined extracts were washed with 50 mL each of water and brine and then dried with magnesium sulfate. Filtration and condensation by rotary evaporation yielded 30.8 gm of compound 12 as a yellow oil which solidified upon standing.

Step 2C: Preparation of compound 13.



To a 1-L round bottom flask equipped with a magnetic stir bar and dropping funnel was added 30 gm of compound 12, 200 mL of methylene chloride, and 5 drops of pyridine. A solution of 29.2 gm of thionyl chloride in 200 mL of methylene chloride was added dropwise. The dropping funnel was then replaced with a reflux condenser and the reaction heated to gentle reflux for 4 hr. The reaction was then condensed by rotary evaporation to yield 31.4 gm of compound 13 as a brown solid. This material was used directly in Step 3 without additional purification.

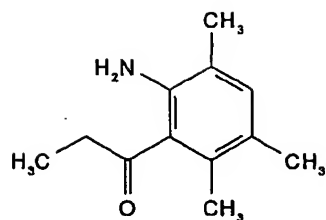
Step 3: Preparation of compound 15.

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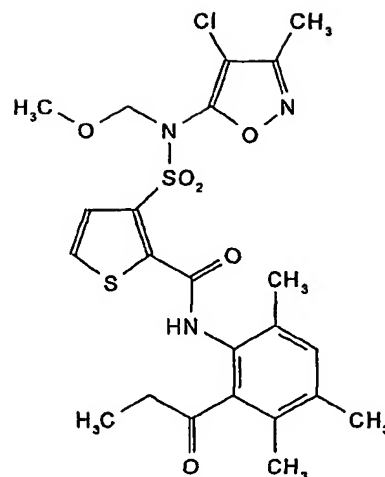
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To a 1-L round bottom flask equipped with a magnetic stir bar and dropping funnel was added 19.8 gm of compound (14) and 150 mL of methylene chloride. To this was added dropwise a solution of 20.0 gm of compound 13 dissolved in 350 mL of methylene chloride. The reaction was stirred at room temperature for 3 hr and then condensed by rotary evaporation. To the residual materials was added 200 mL of ether and the mixture was filtered. The filter cake was washed with 100 mL of ether followed by 2X 200 mL of hot ethyl acetate. The combined washings were washed with 3X 100mL of 1N HCl followed by 100 mL each with water, sat. sodium bicarbonate, and brine. The solution was then dried with magnesium sulfate, filtered, and condensed by rotary evaporation to yield a semi-crystalline material. This material was triturated with 100 mL of ether to yield 20.1 gm of compound 15 as a white solid.

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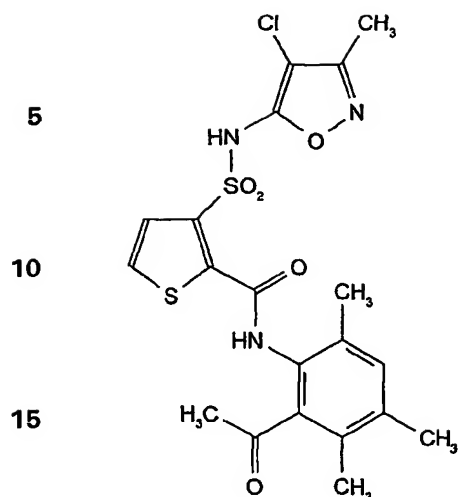
Step 4: Preparation of compound 16.

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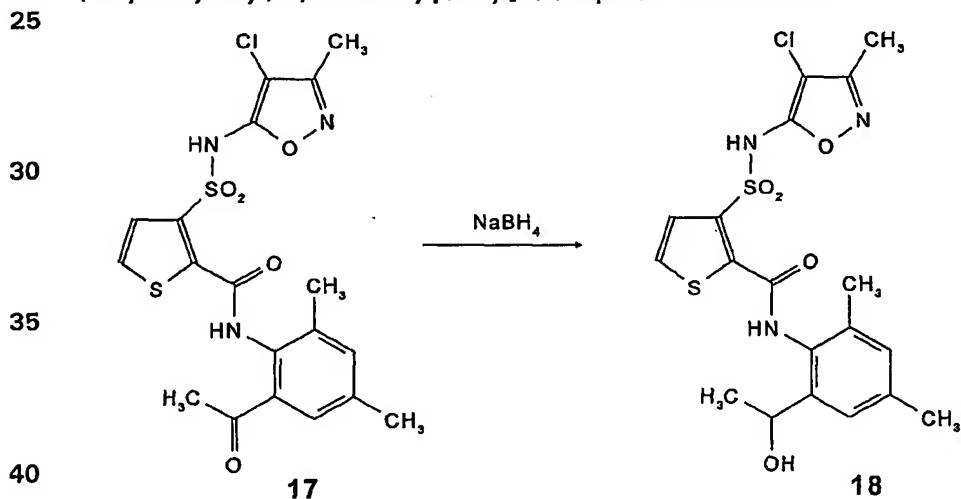
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20 By the procedure of Example 1, Step 4A, compound 15 was converted to compound 16, a solid, mp 166-170 °C.

EXAMPLE 4

25 Preparation of compound 18: 3-[[[4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl]-N-[2-(1-hydroxyethyl)-4,6-dimethylphenyl]-2-thiophene carboxamide



To a solution of 100 mg of compound 17 (sodium salt) in water was added 100 mg of sodium borohydride. After 3 h, an additional 100 mg of sodium borohydride was added and the solution stirred at room temperature overnight. The reaction was mixed with excess saturated ammonium chloride solution, extracted with ethyl acetate (3 x 50

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mL). The extracts were washed with saturated sodium bicarbonate solution and evaporated to give compound 18 (Na salt) as a solid, mp 147-154 °C.

EXAMPLE 5

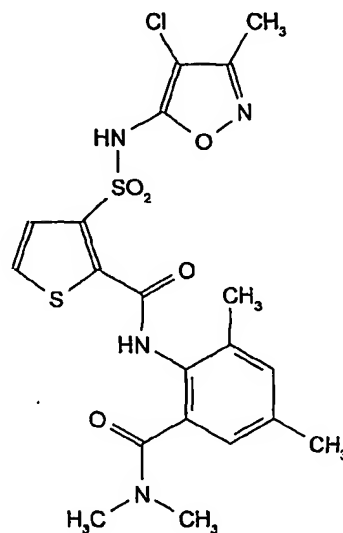
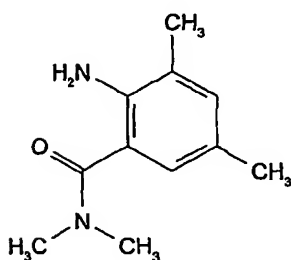
Preparation of compound 20: 3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-{2-
5 [[dimethylamino]carbonyl]-4,6-dimethylphenyl}-2-thiophene carboxamide

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Compound 20 was prepared according to the procedure of Example 3 except that 2-[[dimethylamino]carbonyl]-4,6-dimethylaniline (19) was used in step 3 in the place of compound 12. Compound 20 was obtained as a white solid.

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EXAMPLE 6

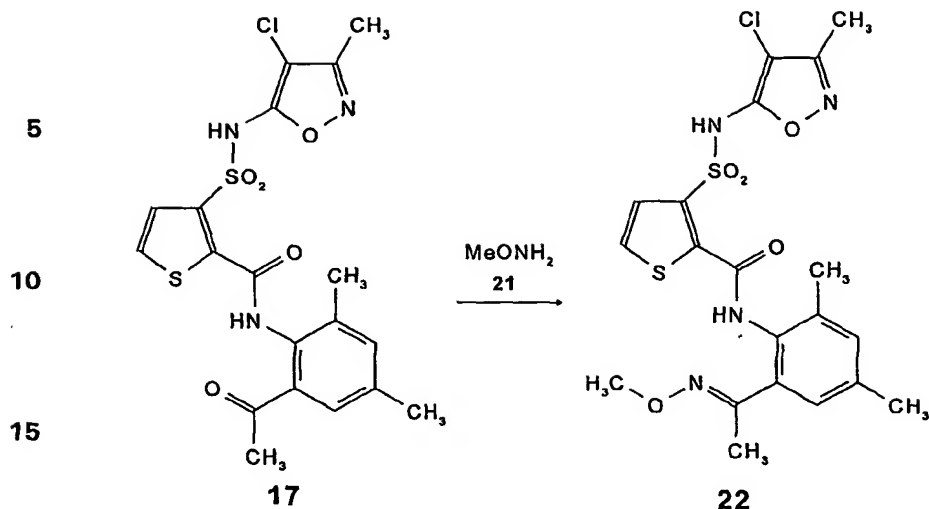
Preparation of compound 22: 3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-
35 {2,4-dimethyl-6-[(methyloxy)ethanimidoyl]phenyl}-2-thiophene carboxamide

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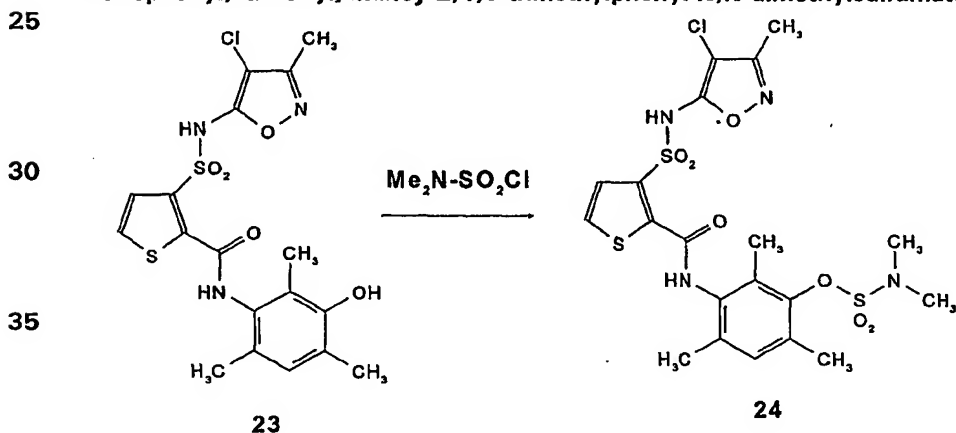
-267-



20 Compound 17 was reacted with methoxyamine (21) in ethanol solution to yield compound 22 as a white solid; mp 140-145 °C.

EXAMPLE 7

Preparation of compound 24: 3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-2-thiophenylcarbamoyl]amino]-2,4,6-trimethylphenyl-N,N-dimethylsulfamate



40 To an ice-cold solution of 700 mg of 3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-[[2-(2,4,6-trimethylphenyl)carbamoyl]amino]-2-thiophenecarboxamide (23) in 15 mL of dimethylformamide was added 247 mg of potassium t-butoxide. After a short period, 317 mg of dimethylaminosulfonyl chloride was added. When the

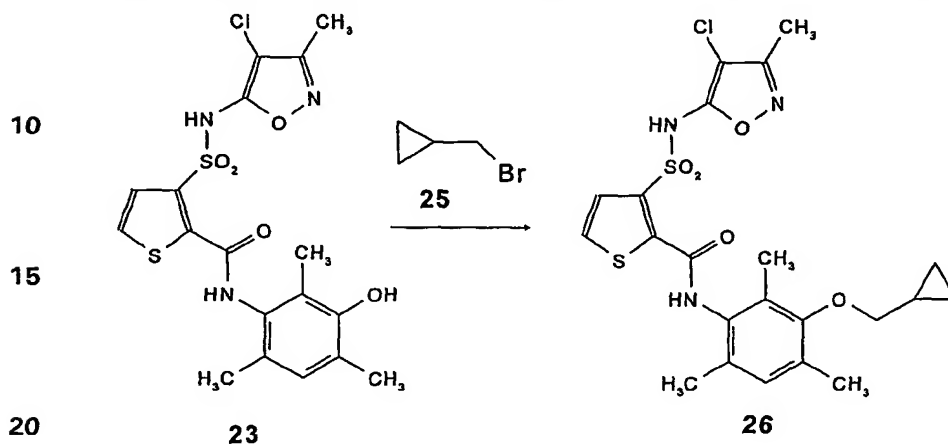
45 reaction was judged complete, it was diluted with water, acidified with 1 N hydrochloric acid. This mixture was extracted with ethyl acetate (3 x 30 mL) and the combined

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extracts were dried (MgSO_4), filtered, and evaporated to yield compound 24 as a white solid; mp 169-174 °C.

EXAMPLE 8

Preparation of compound 26: 3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-{3-[(cyclopropylmethyl)oxy]-2,4,6-trimethylphenyl}-2-thiophenecarboxamide



To an ice-cold solution of 700 mg of 3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-{3-hydroxy-2,4,6-trimethylphenyl}-2-thiophenecarboxamide (23) in 15 mL of dimethylformamide was added 247 mg of potassium t-butoxide. After a short period, 135 mg of cyclopropylmethylbromide (25) was added. When the reaction was judged complete, it was diluted with water, acidified with 1 N hydrochloric acid. This mixture was extracted with ethyl acetate (3 x 30 mL) and the combined extracts were dried (MgSO_4), filtered, and evaporated to yield compound 26 as a white solid; mp 155-158 °C.

EXAMPLE 9

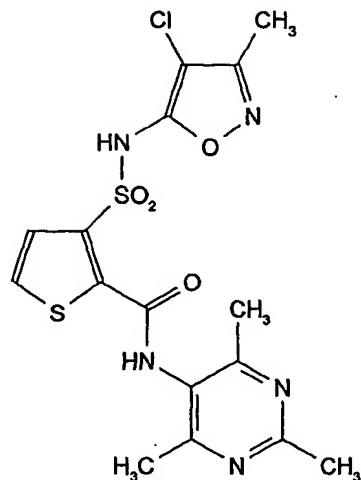
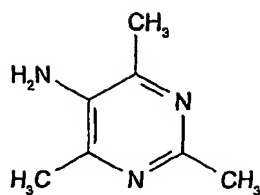
Preparation of compound 28: 3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-(2,4,6-trimethyl-5-pyrimidinyl)-2-thiophenecarboxamide

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Compound 28 was prepared according to the procedure of Example 3 except that 5-amino-2,4,6-trimethylpyrimidine (27) was used in step 3 in the place of compound 12. Compound 28 was obtained as a white solid; mp 170-175 °C.

EXAMPLE 10

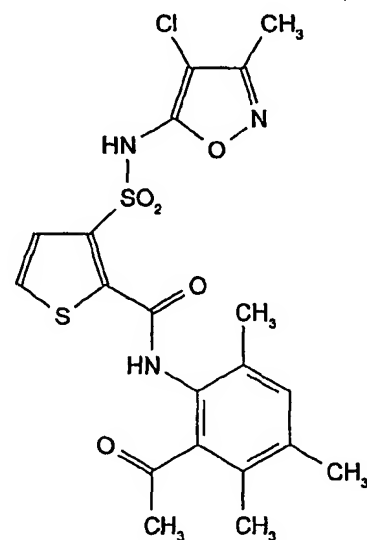
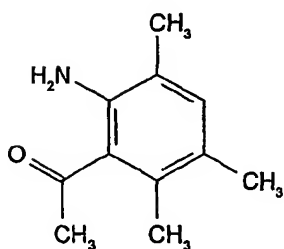
Preparation of compound 30: N-(2-acetyl-3,4,6-trimethylphenyl)-3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-2-thiophenecarboxamide

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Compound 30 was prepared according to the procedure of Example 3 except that 2-acetyl-3,4,6-trimethylaniline (29) was used in step 3 in the place of compound 12. Compound 30 was obtained as a white solid; mp 223-225 °C.

EXAMPLE 11

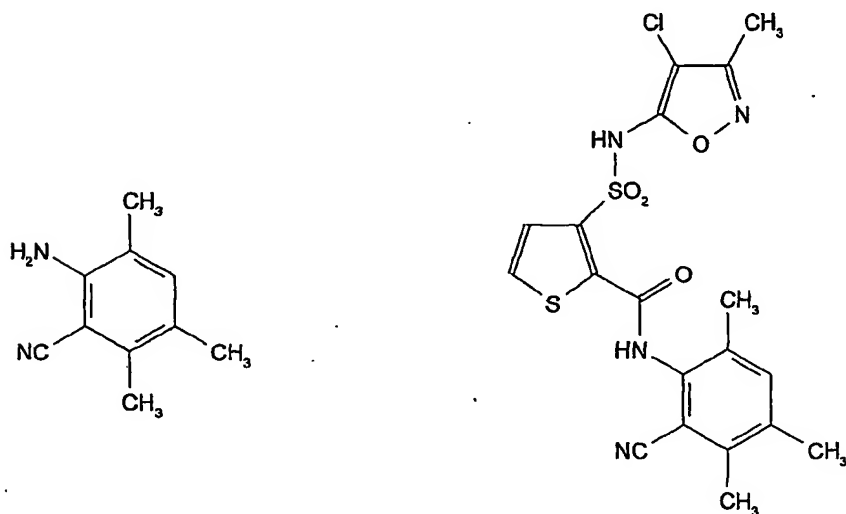
- 5 Preparation of compound 32: 3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-(2-cyano-3,4,6-trimethylphenyl)-2-thiophenecarboxamide

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Compound 32 was prepared according to the procedure of Example 3 except that 2-cyano-3,4,6-trimethylaniline (31) was used in step 3 in the place of compound 30. Compound 32 was obtained as a white solid; mp 218-220 °C.

EXAMPLE 12

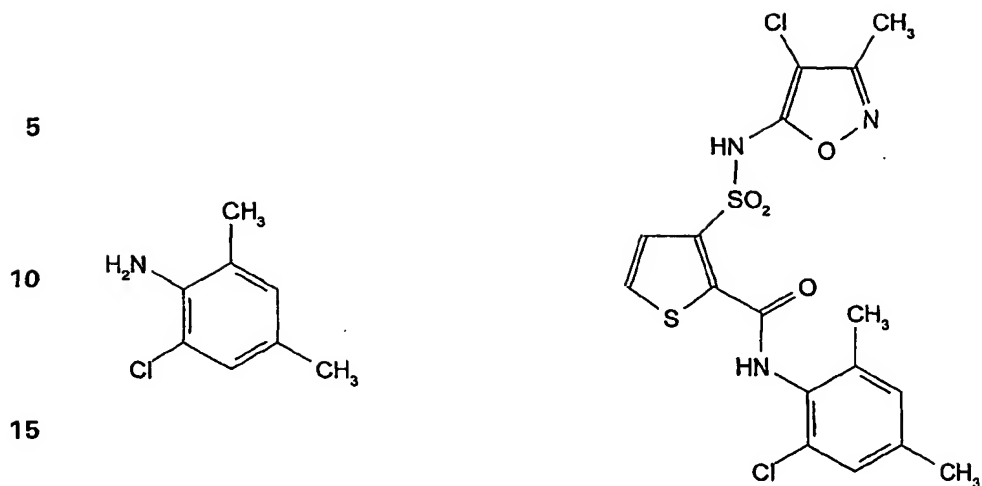
Preparation of compound 34: N-(2-chloro-4,6-dimethylphenyl)-3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-2-thiophenecarboxamide

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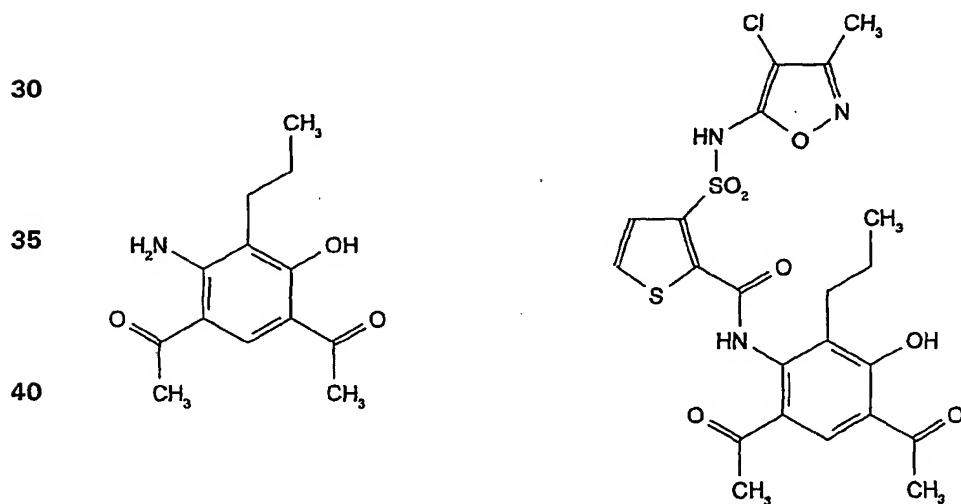
-271-



20 Compound **34** was prepared according to the procedure of Example 3 except that 2-chloro-4,6-dimethylaniline (**33**) was used in step 3 in the place of compound **12**. Compound **34** was obtained as a white solid; mp 174-176 °C.

EXAMPLE 13

25 Preparation of compound **36**: 3-[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl}-N-(4,6-diacetyl-3-hydroxy-2-propylphenyl)-2-thiophenecarboxamide

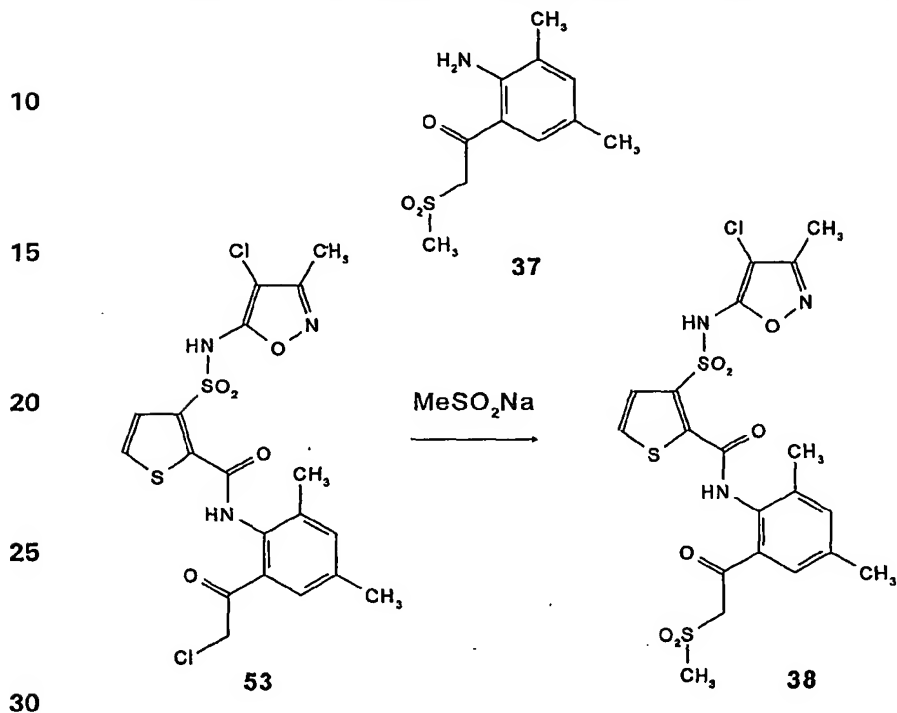


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Compound 36 was prepared according to the procedure of Example 3 except that 4,6-diacetyl-3-hydroxy-2-propylaniline (35) was used in step 3 in the place of compound 12. Compound 36 was obtained as a white solid; mp 163-167 °C.

EXAMPLE 14

- 5 Preparation of compound 38: 3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-(2,4-dimethyl-6-[2-(methylsulfonyl)acetyl]phenyl)-2-thiophenecarboxamide



Intermediate compound 53 was prepared according to the procedure of Example 3 except that 2,4-dimethyl-6-(2-chloroacetyl)aniline (37) was used in step 3 in the place of compound 12.

- 35 A solution of 400 mg of compound 53 and 1.2 g of sodium methanesulfonate in 10 mL of dimethylformamide was stirred at room temperature. When the reaction was judged complete, the reaction was diluted with water, acidified with 2 N hydrochloric acid and extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried (MgSO₄), filtered, and condensed by rotary evaporation to yield compound 38 as a solid;
- 40 mp 172-175 °C.

EXAMPLE 15

Preparation of compound 40: 3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-(2,4-dimethyl-6-{[methyl(2,2-dimethylpropyl)amino]carbonyl}phenyl)-2-thiophenecarboxamide

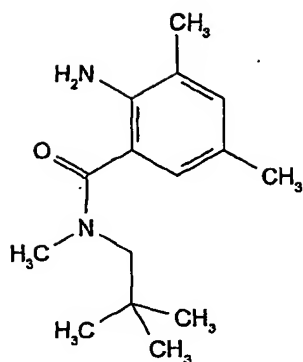
-273-

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Compound **40** was prepared according to the procedure of Example 3 except that 2-[[methyl-(2,2-dimethylpropyl)amino]carbonyl]-4,6-dimethylaniline (**39**) was used in step 3 in the place of compound **12**. Compound **40** was obtained as a white solid; mp 174-176 °C.

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EXAMPLE 16

Preparation of compound **42**: 3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-[2,4-dimethyl-6-(methylsulfonyl)phenyl]-2-thiophenecarboxamide

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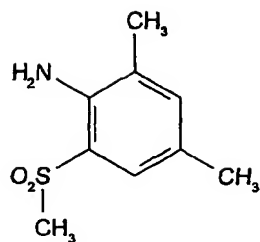
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Compound **42** was prepared according to the procedure of Example 3 except that 2,4-dimethyl-6-(methylsulfonyl)aniline (**41**) was used in step 3 in the place of compound **12**. Compound **42** was obtained as a white solid; mp 208-210 °C.

EXAMPLE 17

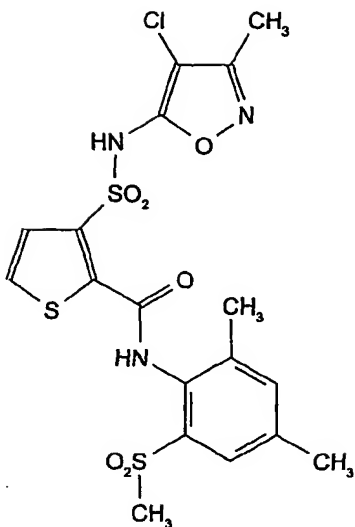
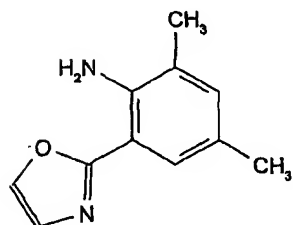
25 Preparation of compound **44**: 3-{[(4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl}-N-[2,4-dimethyl-6-(1,3-oxazol-2-yl)phenyl]-2-thiophenecarboxamide

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Compound 44 was prepared according to the procedure of Example 3 except that 2,4-dimethyl-6-(1,3-oxazol-2-yl)aniline (43) was used in step 3 in the place of compound 12. Compound 44 was obtained as a white solid; mp 176-178 °C.

EXAMPLE 18

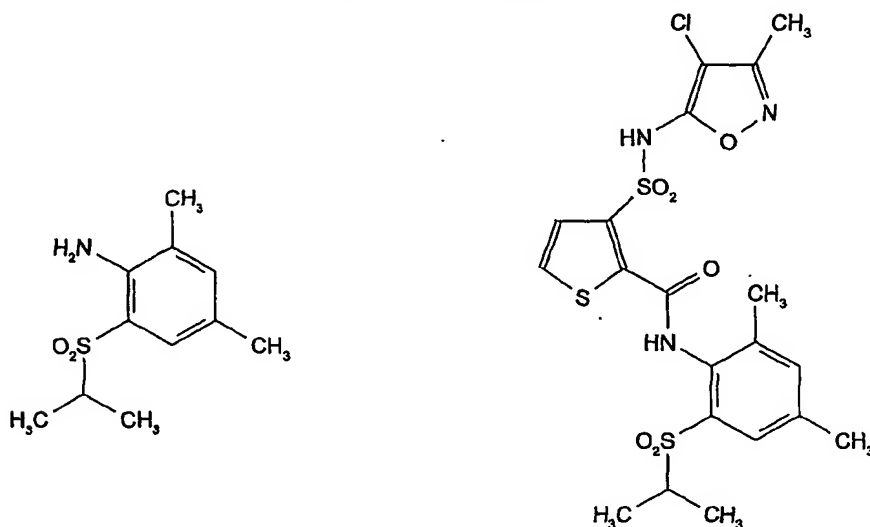
- 5 Preparation of compound 46: 3-[[[4-chloro-5-isoxazolyl)amino]sulfonyl]-N-[2-(2-propylsulfonyl)-4,6-dimethylphenyl]-2-thiophenecarboxamide

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Compound 46 was prepared according to the procedure of Example 3 except that 2-(2-propylsulfonyl)-4,6-dimethylaniline (45) was used in step 3 in the place of compound 12. Compound 46 was obtained as a white solid; mp 190-192 °C.

EXAMPLE 19

- 30 Preparation of compound 48: 3-[[[4-chloro-3-methyl-5-isoxazolyl)amino]sulfonyl]-N-[2,4-dimethyl-6-(propylsulfonyl)phenyl]-2-thiophenecarboxamide

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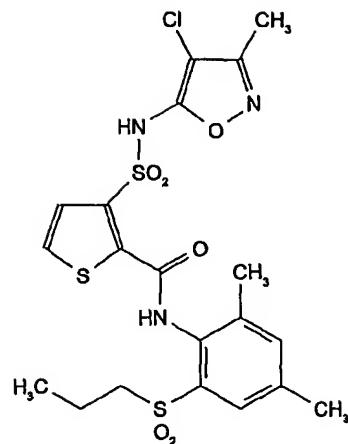
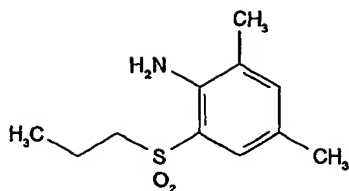
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Compound 48 was prepared according to the procedure of Example 3 except that 2,4-dimethyl-6-(propylsulfonyl)aniline (47) was used in step 3 in the place of compound 12. Compound 48 was obtained as a white solid; mp 152-155 °C.

EXAMPLE 20

Preparation of compound 50: 3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-(2-ethyl-4,6-dimethylphenyl)-2-thiophenecarboxamide

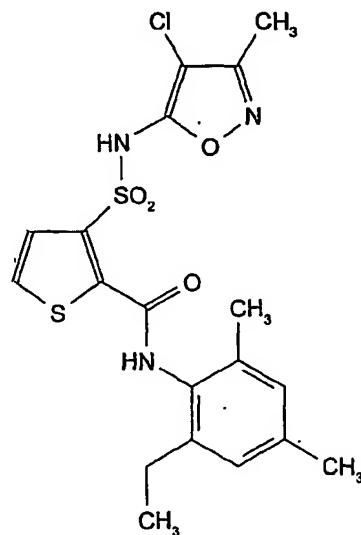
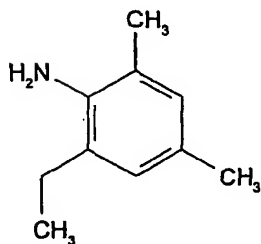
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Compound 50 was prepared according to the procedure of Example 3 except that 2-ethyl-4,6-dimethylaniline (49) was used in step 3 in the place of compound 12. Compound 50 was obtained as a white solid; mp 152-154 °C.

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EXAMPLE 21

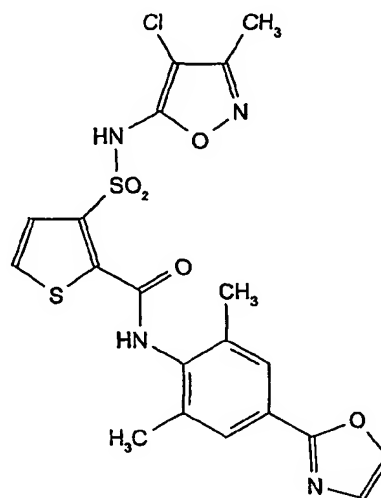
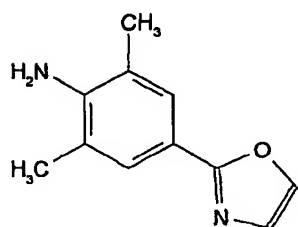
Preparation of compound 52: 3-[[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-N-[2,6-dimethyl-4-(1,3-oxazol-2-yl)phenyl]-2-thiophenecarboxamide

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Compound 52 was prepared according to the procedure of Example 3 except that 2,6-dimethyl-4-(1,3-oxazol-2-yl)aniline (51) was used in step 3 in the place of compound 12. Compound 52 was obtained as a white solid; mp 205-207 °C.

EXAMPLE 22

Method for testing for compounds that possess anti-laminitic activity

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Compounds and compositions for use in the treatment, prevention, or amelioration of one or more symptoms of laminitis can be and were identified by comparison with controls in foundered horses. The horses are evaluated for lameness, hoof wall temperature. Hoof wall temperature is used to index the digital perfusion in the experiment. An increase in hoof wall temperature compared to control indicates increased digital blood flow, and that the ischemic crisis is not as severe in the developmental phase of the disorder.

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Material and methods

Eighteen healthy horses were used in the study. These horses were divided into Group A (ten horses) and Group B (eight horses). Group A horses served as placebo controls and Group B horses received treatment. All subjects used in the study were evaluated to ensure that digits were within normal limits (clinical evaluation and

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radiographs) and were trained to stand quietly in an instrumented stanchion containing force plates.

At the initiation of the experiment, the fore digits of the subjects were instrumented with skin surface thermistors and the hoof wall temperature and force plate loading parameters were collected. Force plate data was recorded for 5 minutes at a 0.01-second interval. The force plates were used to record the load voluntarily placed on each digit. These individual digital loads were summated to determine the weight of the horse, and the percentage of the total load on each digit was calculated. The mean percent of the total load placed on each digit (% load) and one standard deviation of the percent load (load distribution profile) were recorded and used as parameters in the study.

The experimental subjects were sex and age matched. Assignment to Group A or B was done randomly. Each pair was brought into the temperature (72 °F) and humidity (42%) controlled laboratory environment for a period of 24 hours. During this time, the horses were evaluated at 4-hour intervals to establish control data for each horse. At each 4-hour sampling period, the horses were brought into the measurement laboratory, which was immediately adjacent to and at the same environmental conditions as the stalls. Measurement parameters collected consisted of hoof wall temperature, mean % load, load distribution profile, and physical symptoms (presence of lameness). In addition, the horses were videotaped in their stalls during the entire 72 hours of the experiment. These tapes were reviewed to determine the horse's physical status and the amount of time that the horses were standing versus lying down.

The horses (one treated and one placebo) received a laminitis-inducing diet by nasogastric tube within 30 minutes of each other. This diet is 85% cornstarch, 15% methyl-cellulose mix administered at 17.6 g/kg of body weight. Following administration of the diet the horses were followed at 4-hour intervals using the same sampling protocol as described above. At each sampling period the hoof wall temperature was plotted to determine the occurrence of a bilateral decrease in the hoof wall temperature relative to control temperature for each animal. At this point the horses in Group A received a placebo and the Group B horses received the endothelin antagonist N-(4-chloro-3-methyl-5-isoxazolyl)-2-[[3,4-(methylenedioxy)-6-methylphenyl]-acetyl]-thiophene-3-sulfonamide, also designated 4-chloro-3-methyl-5-(2-[2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl]-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-

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methyl-5-isoxazoly]-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide, via an intravenous catheter at a dose of 10 mg/kg, SID for the next 48 hours.

Following treatment the subjects were returned to their stalls and monitoring was continued at the same 4-hour intervals described above. At the end of the 72
5 hours the horses were evaluated for lameness and returned to their stalls. Similarly, each horse was examined for lameness once a day for three additional days. The severity of lameness was determined subjectively (Obel Grading) and by force plate evaluation. Eight hours following onset of lameness, or eight hours from the termination of the experiment if the horse did not develop lameness, a dorsal submural biopsy was
10 obtained. This was completed under local anesthesia. Samples were stained and examined for the integrity of the laminar epithelium and basal cell/basement membrane. At the termination of the experiment the horses were placed on systemic analgesics (phenylbutazone 2.2 mg/kg) if necessary and allowed to recover.

Data analysis and interpretation

15 Digital temperature data was plotted and used to grade the severity of the digital ischemia. The force plate parameters (mean % load and load distribution profile) were used to grade the severity of lameness if present. Digital temperatures and force plate parameters from treated, placebo, and non-treated control horses were compared statistically (one way ANOVA).

20 Results

Clinical status and recovery following treatment

Five of the placebo treated horses (Group A) were clinically recovered from their lamenesses by 72 hours, 2 were still lame, and 3 demonstrated a persistent lameness. In the treated horses (Group B), 6 were fully recovered at 72 hours, 2 demonstrated
25 lameness at 72 hours, and none demonstrated persistent lameness. These data indicate a strong trend that the endothelin antagonist enhanced the recovery from the acute insult ($p = 0.0608$).

Digital Blood Flow

The temperature data was examined and separated into one of three patterns.
30 The first pattern reflected a mild, transient decrease in the hoof wall temperature that lasted less than 4 to 8 hours. The second pattern was that of a decreased temperature of 4-5 °C that lasted less than 4 to 8 hours. The third pattern was that of a decreased temperature of 4 to 5 °C that persisted for 10 to 12 hours. As the hoof wall temperature was used to index digital perfusion in this experiment, and served as the

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point in time when treatment with the endothelin antagonist was initiated, these three patterns index drug effectiveness in this regard. In the treated horses (Group B), five (62.5%) demonstrated the first pattern, 2 (25%) demonstrated pattern 2, and only 1 (12.5%) demonstrated pattern 3. In the placebo treated horses (Group A), only 1 (12.5%) demonstrated pattern one, 3 (37.5%) demonstrated the second pattern, and 4 (50%) demonstrated a significant and prolonged decrease in digital perfusion (pattern 3). Statistical comparisons (Wilcoxon rank-sum) between the treated (Group B) and placebo (Group A) horses indicated that they were different ($p = 0.0039$).

EXAMPLE 23

10 Assays for identifying compounds that exhibit endothelin antagonistic and/or agonist activity

Compounds that are potential endothelin antagonists are identified by testing their ability to compete with ^{125}I -labeled ET-1 for binding to human ET_A receptors or ET_B receptors present on isolated cell membranes. The effectiveness of the test compound as an antagonist or agonist of the biological tissue response of endothelin can also be assessed by measuring the effect on endothelin induced contraction of isolated rat thoracic aortic rings. The ability of the compounds to act as antagonists or agonists for ET_B receptors can be assessed by testing the ability of the compounds are to inhibit endothelin-1 induced prostacyclin release from cultured bovine aortic endothelial cells.

20 A. Endothelin binding inhibition - Binding Test #1: Inhibition of binding to ET_A receptors

TE 671 cells (ATCC Accession No. HTB 139) express ET_A receptors. These cells were grown to confluence in T-175 flasks. Cells from multiple flasks were collected by scraping, pooled and centrifuged for 10 min at 190 X g. The cells were re-suspended in phosphate buffered saline (PBS) containing 10 mM EDTA using a Tenbroeck homogenizer. The suspension was centrifuged at 4° C at 57,800 X g for 15 min, the pellet was resuspended in 5 ml of buffer A (5 mM HEPES buffer, pH 7.4 containing aprotinin (100 KIU/ml)) and then frozen and thawed once. 5 ml of Buffer B (5 mM HEPES Buffer, pH 7.4 containing 10 mM MnCl_2 and 0.001% deoxyribonuclease Type 1) was added, the suspension mixed by inversion and then incubated at 37° C for 30 minutes. The mixture was centrifuged at 57,800 X g as described above, the pellet washed twice with buffer A and then resuspended in buffer C (30 mM HEPES buffer, pH 7.4 containing aprotinin (100 KIU/ml) to give a final protein concentration of 2 mg/ml and stored at -70° C until use.

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The membrane suspension was diluted with binding buffer (30 mM HEPES buffer, pH 7.4 containing 150 mM NaCl, 5mM MgCl₂, 0.5% Bacitracin) to a concentration of 8 µg/50 µl. ¹²⁵I-endothelin-1 (3,000 cpm, 50 mL) was added to 50 µL of either: (A) endothelin-1 (for non specific binding) to give a final concentration 80 nM); (B) binding buffer (for total binding); or (C) a test compound (final concentration 1 nM to 100 µM). The membrane suspension (50 µL), containing up to 8 µg of membrane protein, was added to each of (A), (B), or (C). Mixtures were shaken, and incubated at 4° C for 16-18 hours, and then centrifuged at 4° C for 25 min at 2,500 X g. Alternatively, the incubation was conducted at 24° C. When incubated at 24° C, the IC₅₀ concentrations are 2- to 10-fold higher than when the incubation is conducted at 4° C. This, must be kept in mind when comparing IC₅₀ concentrations among compounds provided herein.

The supernatant, containing unbound radioactivity, was decanted and the pellet counted on a Genesys multiwell gamma counter. The degree of inhibition of binding (D) was calculated according to the following equation:

$$\% D = 100 - \frac{(C) - (A)}{(B) - (A)} \times 100$$

Each test was generally performed in triplicate.

20 **B. Endothelin binding inhibition - Binding Test #2: Inhibition of binding to ET_B receptors**

COS7 cells were transfected with DNA encoding the ET_B receptor, The resulting cells, which express the human ET_B receptor, were grown to confluence in T-150 flasks. Membrane was prepared as described above. The binding assay was performed as described above using the membrane preparation diluted with binding buffer to a concentration of 1 µg/50 µl.

Briefly, the COS7 cells, described above, that had been transfected with DNA encoding the ET_B receptor and express the human ET_B receptor on their surfaces were grown to confluence in T-175 flasks. Cells from multiple flasks were collected by scraping, pooled and centrifuged for 10 min at 190 X g. The cells were resuspended in phosphate buffered saline (PBS) containing 10 mM EDTA using a Tenbroeck homogenizer. The suspension was centrifuged at 4° C 57,800 X g for 15 min, the pellet was resuspended in 5 ml of buffer A (5mM HEPES buffer, pH 7.4 containing aprotinin (100 KIU/ml)) and then frozen and thawed once. Five ml of Buffer B (5 mM HEPES Buffer, pH 7.4 containing 10 mM MnCl₂ and 0.001% deoxyribonuclease Type 1) was

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added, the suspension mixed by inversion and then incubated at 37° C for 30 minutes. The mixture was centrifuged at 57,800 X g as described above, the pellet washed twice with buffer A and then resuspended in buffer C (30 mM HEPES buffer, pH 7.4 containing aprotinin (100 KIU/ml) to give a final protein concentration of 2 mg/ml.

- 5 The binding assay was performed as described above using the membrane preparation diluted to give 1 µg/50 µl of binding buffer.

C. Test for activity against endothelin-induced contraction of isolated rat thoracic aortic rings

- 10 The effectiveness of the test compound as an antagonist or agonist of the biological tissue response of endothelin also is assessed by measuring the effect on endothelin induced contraction of isolated rat thoracic aortic rings (see, e.g., Borges et al. (1989) Eur. J. Pharmacol. 165:223-230) or by measuring the ability to contract the tissue when added alone.

- 15 Compounds to be tested are prepared as 100 µM stocks. If necessary to effect dissolution, the compounds are first dissolved in a minimum amount of DMSO and diluted with 150 mM NaCl. Because DMSO can cause relaxation of the aortic ring, control solutions containing varying concentrations of DMSO were tested.

- 20 The thoracic portion of the adult rat aorta is excised, the endothelium abraded by gentle rubbing and then cut into 3 mm ring segments. Segments are suspended under a 2 g preload in a 10 ml organ bath filled with Krebs'- Henseleit solution saturated with a gas mixture of 95% O₂ and 5% CO₂ (118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 25 mM NaHCO₃, 2.5 mM CaCl₂, 10 mM D-glucose).

- 25 There is a correlation between activity as an antagonist of endothelin-induced thoracic aortic ring contraction and activity as an inhibitor of binding of endothelin to endothelin receptors. The pA₂ is a linear function of the log of the IC₅₀.

D. Assay for identifying compounds that have agonist and/or antagonistic activity against ET_B receptors

1. Stimulation of prostacyclin release

- 30 Since endothelin-1 stimulates the release of prostacyclin from cultured bovine aortic endothelial cells, the compounds that have agonist or antagonist activity are identified by their ability to inhibit endothelin-1 induced prostacyclin release from such endothelial cells by measuring 6-keto PGF_{1α} substantially as described by (Filep et al. (1991) Biochem. Biophys. Res. Commun. 177 171-176. Bovine aortic cells are obtained from collagenase-treated bovine aorta, seeded into culture plates, grown in
- 35 Medium 199 supplemented with heat inactivated 15% fetal calf serum, and L-glutamine

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(2 mM), penicillin, streptomycin and fungizone, and subcultured at least four times. The cells are then seeded in six-well plates in the same medium. Eight hours before the assay, after the cells reach confluence, the medium is replaced. The cells are then incubated with a) medium alone, b) medium containing endothelin-1 (10 nM), c) test compound alone, and d) test compound + endothelin-1 (10 nM).

After a 15 min incubation, the medium is removed from each well and the concentrations of 6-keto PGF_{1 α} are measured by a direct immunoassay. Prostacyclin production is calculated as the difference between the amount of 6-keto PGF_{1 α} released by the cells challenged with the endothelin-1 minus the amount released by identically treated unchallenged cells. Compounds that stimulate 6-keto PGF_{1 α} release possess agonist activity and those which inhibit endothelin-1 6-keto PGF_{1 α} release possess antagonist activity.

2. Inhibition of sarafotoxin 6c induced contraction

Sarafotoxin 6c is a specific ET_B antagonist that contracts rat fundal stomach strips. The effectiveness of tests compounds to inhibit this sarafotoxin 6c-induced contraction of rat fundal stomach strips is used as a measure ET_B antagonist activity. Two isolated rat fundal stomach strips are suspended under a 1 g load in a 10 ml organ bath filled with Krebs'-Henseleit solution containing 10 μ M cyclo(D-Asp-Pro-D-Val-Leu-D-Trp) (BQ-123; see, U.S. Patent No. 5,114,918 to Ishikawa *et al.*), 5 μ M indomethacin, and saturated with a gas mixture of 95% O₂/5% CO₂. Changes in tension are measured isometrically and recorded using a Grass Polygraph coupled to a force transducer. Sarafotoxin 6c is added cumulatively to one strip while the second strip is preincubated for 15 min with a test compound prior to addition of cumulative doses of sarafotoxin 6c. The effects of the test compounds on the concentration-response curve for sarafotoxin 6c are examined.

E. Deoxycorticosterone acetate (DOCA)-salt hypertensive rat model for assessing *in vivo* activity of selected compounds

Selected compounds disclosed herein have been tested for activity in the deoxycorticosterone acetate (DOCA)-salt hypertensive rat model. To perform these tests, silastic MDX4-4210 elastomer implants containing 47 mg (DOCA) were prepared according to the method of Ormsbee *et al.* ((1973) the *J. Pharm. Sci.* 62:255-257). Briefly, DOCA is incorporated into silicon rubber implants for sustained release. To prepare the implants the DOCA is incorporated into unpolymerized silicone rubber, catalyst is added and the mixture is cast in a hemicylindrical shape.

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Sprague Dawley rats (7-8 weeks old) were unilaterally nephrectomized under ketamine anesthesia and a DOCA-implant was placed on the left lateral dorsal abdomen of the animal. The rats were allowed to recover for three weeks. During recovery they were permitted free access to normal rat chow and 0.9% NaCl drinking solution in place of drinking water. The rats develop hypertension within 3 weeks.

All animals were used in the tests between 21 and 30 days post surgery. The mean arterial blood pressure in these animals ranged from 165-200 mm Hg.

On the day of experimentation, catheters were inserted under brevitall anesthesia into the right femoral artery for measurement of blood pressure, and into the right femoral vein for administration of a selected compound. The animals were placed in a restrainer and allowed to recover for a minimum of 60 min or until a steady mean arterial blood pressure was recorded. At that time, the selected compound or control vehicle was administered either intravenously, as a 60 minute infusion, or orally by oral gavage. Blood pressure was recorded continuously for a further 10 hrs.

F. Effect of Intravenous administration on ET-1-induced pressor responses in conscious, autonomically blocked rats; a model for assessing in vivo activity of selected compounds

Male Sprague Dawley rats (250-450 g) were anesthetized (Brevital 50 mg/kg, IP) and cannulae were placed in the femoral artery to measure mean arterial pressure (MAP) and in the femoral vein for intravenous drug administration. Animals were placed in a restrainer and allowed to regain consciousness. Thirty minutes later autonomic blockade was administered (atropine methyl nitrate, 3 mg/kg, IV, followed by propranolol, 2 mg/kg, IV). An hour later animals received a bolus injection of vehicle (0.5 ml) followed thirty minutes later by intravenous bolus administration of ET-1 (Control, 1 μ g/kg). Following recovery from this challenge, test -compounds were administered by intravenous bolus administration (0.5 ml) and then re-challenged with ET-1 thirty minutes later. Results are expressed as the percent inhibition of the ET-1-induced pressor response after administration of the test compound compared to the pressor response induced by the control ET-1 challenge. In some cases a third ET-1 challenge was administered ninety minutes after administration of the test compound.

G. Results

1. In vitro

The IC_{50} for each of the compounds of the preceding Examples for ET_A and ET_B receptors has been measured. Almost all of the compounds have an IC_{50} of less than 10 μ M for either or both of the ET_A and ET_B receptors. Many of the compounds have an

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IC₅₀ less than about 10 μ M, others have an IC₅₀ less than about 1 μ M and some of the compounds have an IC₅₀ less than about 0.1 μ M. A number of the compounds have an IC₅₀ for ET_A receptors that is substantially less (10 to 100-fold or more) than for ET_B receptors, and, thus are selective for ET_A receptors. Others of the compounds are ET_B selective.

2. In vivo

- a. Selected compounds, such as N-(4-chloro-3-methyl-5-isoxazolyl)-2-(N-(4-methyl-phenyl)aminocarbonyl)thiophene-3-sulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)benzyl]benzo[b]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3,4-methylenedioxy)benzyl]benzo[b]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[β -hydroxy(3,4-methylenedioxy)phenylethyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide and N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3,4-methylenedioxybenzylcarbonyl)thiophene-3-sulfonamide, have been tested in the hypertensive rat model, and were effective in decreasing blood pressure.
- b. Selected compounds, such as N-(4-chloro-3-methyl-5-isoxazolyl)-2-([3,4-(methylenedioxy)phenyl]acetyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-([2-acetyl-4,5-(methylenedioxy)phenyl]aminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-([4-methoxy-2-methylphenyl]aminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-cyano-4,5-dimethoxyphenyl]aminocarbonyl]thiophene-3-sulfonamide, and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide have been tested in the autonomically blocked, normotensive rat model and shown to have substantial activity, reducing pressure about 30% in 30 min at dosages as low as 30 mg/kg, and more than 50% at dosages of 60 mg/kg. On the average dosages of 30-60 mg/kg of the test compound resulted in a 40-60% inhibition of pressor response.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

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WHAT IS CLAIMED IS:

1. A method of treating, preventing, or ameliorating one or more symptoms of laminitis, comprising administering to a hooved animal an effective amount of an endothelin receptor antagonist or a veterinarily acceptable derivative thereof.

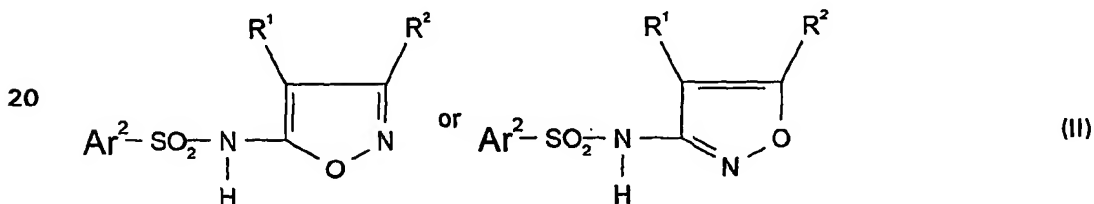
5 2. The method of claim 1, wherein the laminitis is equine or bovine laminitis.

3. The method of claim 1 or claim 2, further comprising administering an effective amount of (i) a nitric oxide synthase substrate; or (ii) a nitric oxide donor.

4. The method of claim 3, wherein:
 10 the nitric oxide synthase substrate is L-arginine; and
 the nitric oxide donor is sodium nitroprusside, nitroglycerin, glyceryl trinitrate, SIN-1, isosorbidmononitrate or isosorbiddinitrate.

5. The method of any one of claims 1 to 5, wherein the endothelin receptor antagonist is a sulfonamide or a veterinarily acceptable derivative thereof.

15 6. The method of any one of claims 1 to 5, wherein the endothelin receptor antagonist is a sulfonamide compound of formula II:



25 or a veterinarily acceptable derivative thereof, wherein, R¹ and R² are either (i), (ii) or (iii) as follows:

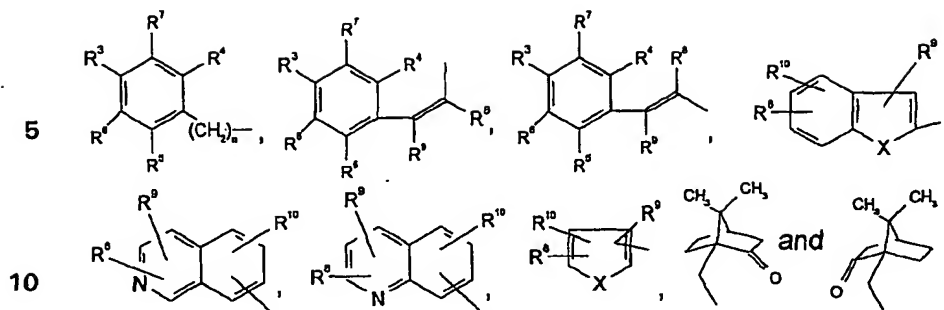
(i) R¹ and R² are independently selected from H, NH₂, NO₂, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino,
 30 hydroxyalkyl, alkoxyalkyl, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms and are either straight or branched chains
 35 or cyclic, and the aryl portions contain from about 4 to about 16 carbons; or,

(ii) R¹ and R² together form -(CH₂)_n, where n is 3 to 6; or,

(iii) R¹ and R² together form 1,3-butadienyl;

Ar² selected from: alkyl,

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- wherein n is 0 to 10, X is O, S or NR^{11} , where R^{11} , which is hydrogen or contains up to about 30 carbon atoms, and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{15}$ and $S(O)_nR^{15}$ in which n is 0-2; R^{15} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R^{11} and R^{15} are unsubstituted or are substituted with one or more substituents each selected
- 20 independently from Z , which is halide, pseudoaldehyde, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{16}$, CO_2R^{16} , SH, $S(O)_nR^{16}$ in which n is 0-2, NHOH, $NR^{12}R^{16}$, NO_2 , N_3 , OR^{16} , $R^{12}NCOR^{16}$ and $CONR^{12}R^{16}$; R^{16} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R^{12} , which is selected independently
- 25 from R^{11} and Z , is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{17}$ and $S(O)_nR^{17}$ in which n is 0-2; and R^{17} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R^{11} , R^{12} , R^{15} and R^{16} are optionally further substituted with any of the groups set forth for Z ;
- 30 R^3 , R^4 , R^5 , R^6 and R^7 are each selected independently from (i)-(iv):
- (i) R^3 , R^4 , R^5 , R^6 and R^7 are each selected independently from among H, NHOH, NH_2 , NO_2 , N_3 , aminoalkyl, alkylamino, dialkylamino, carboxyl, carbonyl, hydroxyl, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, heterocycle, alkoxy, alkylthio, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylalkoxy, aryloxy, arylamino, arylthio, arylsulfinyl,
- 35 arylsulfonyl, haloalkyl, haloaryl, haloalkoxy, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido in which each of the preceding groups are unsubstituted or substituted with groups such as H, NH_2 , NO_2 , alkyl, halide, and pseudohalide; or, alternatively,

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(ii) R^4 and R^7 together are substituted or unsubstituted 1, 3-butadienyl, 1-chloro-1,3-butadienyl, 4-dimethylamino-1,3-butadienyl, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R^3 , R^5 and R^6 are as defined in (i) above; or alternatively,

(iii) R^7 and R^3 together are substituted or unsubstituted 1, 3-butadienyl, 4-dimethylamino-1,3-butadienyl, 1-chloro-1,3-butadienyl, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R^4 , R^5 and R^6 are as defined in (i) above; or alternatively,

(iv) R^3 , R^5 , and R^7 are H; and R^4 and R^6 are each independently selected from alkyl, alkoxy, halide, amino and aminoalkyl; and

R^8 , R^9 , R^{10} are each independently selected as follows from (i) or (ii):

(i) R^8 , R^9 and R^{10} , which each contain hydrogen or up to about 50 carbon atoms, are each independently selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{18}$, CO_2R^{18} , SH, $S(O)_nR^{18}$ in which n is 0-2, HNOH, $NR^{18}R^{19}$, NO_2 , N_3 , OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}$, in which R^{19} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{20}$, $S(O)_nR^{20}$ in which n is 0-2; and R^{18} and R^{20} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; and any of the groups set forth for R^8 , R^9 and R^{10} are unsubstituted or substituted with any substituents set forth for Z, which is halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{21}$, CO_2R^{21} , SH, $S(O)_nR^{21}$ in which n is 0-2, HNOH, $NR^{22}R^{21}$, NO_2 , N_3 , OR^{21} , $R^{22}NCOR^{21}$ and $CONR^{22}R^{21}$; R^{22} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_nR^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; or

(ii) any two of R^8 , R^9 and R^{10} form an aryl, aromatic ring, heteroaromatic ring, alicyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, that is unsubstituted or substituted with one or more substituents in each each substituent is independently selected from Z; and the other of R^8 , R^9 and R^{10} is selected as in (i).

7. The method of claim 6 in which Ar^2 is selected from alkyl, naphthyl, biphenyl, and phenyl.

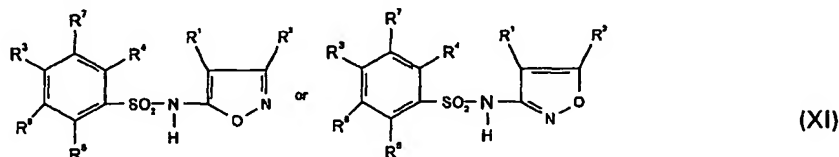
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8. The method of claim 6 in which Ar² is selected from thienyl, furyl, pyrrolyl, 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl and pyrrolidinyl.

9. The method of claim 6 or claim 7, wherein Ar² is naphthyl, phenyl or biphenyl, and the compounds have the formulae:

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in which n is 0 to 10; R³, R⁴, R⁵, R⁶, and R⁷ are selected from (i), (ii), (iii) or (iv):

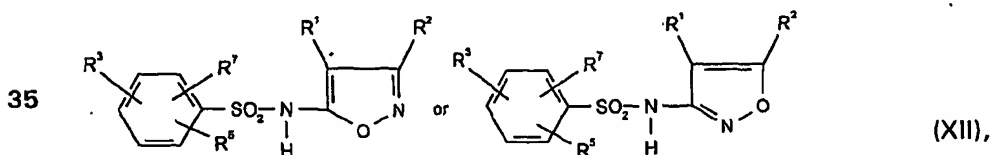
(i) R³, R⁴, R⁵, R⁶, and R⁷ are each selected independently from among H, NHOH, NH₂, NO₂, N₃, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, where the alkyl, alkenyl, alkynyl portions are straight or branched chains of from about 1 up to about 10 carbons, and the aryl portions contain from 3 up to about 10 carbons; or, alternatively,

(ii) R⁴ and R⁷ together are substituted or unsubstituted 1, 3-butadienyl, 4-dimethylamino-1,3 butadiene, 1-chloro-1,3-butadiene, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R³, R⁵ and R⁶ are as defined in (i) above; or alternatively,

(iii) R⁷ and R³ together are substituted or unsubstituted 1, 3-butadienyl, 4-dimethylamino-1,3 butadiene, 1-chloro-1,3-butadiene, 1-aza-1,3-butadienyl or 2-aza-1,3-butadienyl groups; and R⁴, R⁵ and R⁶ are as defined in (i) above; or

(iv) R³, R⁵, and R⁷ are H; and R⁴ and R⁶ are each independently selected from alkyl, alkoxy, halide, aminoalkyl, dialkylaminoalkyl, in which the alkyl and alkoxy groups contain from 1 to 10, and are straight or branched chains.

10. The method of any one of claims 6, 7 or 9 in which Ar² is phenyl and biphenyl and the compound has the formulae (XII):



wherein:

R³, R⁵ and R⁷ are each independently

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- (a) hydrogen, except that at least one of R^3 , R^5 and R^7 is other than hydrogen;
- (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, or aralkoxy, any of which may be substituted with W^1 , W^2 and W^3 , except that if one of R^3 , R^5 or R^7 is alkyl at the 4 position, at least one of the other two of R^3 , R^5 or R^7 is not hydrogen;
- (c) halo;
- (d) hydroxyl;
- (e) cyano;
- (f) nitro, except that if one of R^3 , R^5 and R^7 is 4- NO_2 , then at least one of the other two of R^3 , R^5 and R^7 is not hydrogen;
- (g) $-\text{C}(\text{O})\text{H}$ or $-\text{C}(\text{O})\text{R}^{27}$;
- (h) $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^{27}$;
- (i) $-\text{SH}$, $-\text{S}(\text{O})_n\text{R}^{27}$, $-\text{S}(\text{O})_m-\text{OH}$, $-\text{S}(\text{O})_m-\text{OR}^{27}$, $-\text{O}-\text{S}(\text{O})_m\text{OH}$, or $-\text{O}-\text{S}(\text{O})_m\text{OR}^{27}$;
- (j) $-\text{W}^4\text{NR}^{28}\text{R}^{29}$, except that, if one of R^3 , R^5 and R^7 is 4- $\text{W}^4\text{NR}^{28}\text{R}^{29}$ then at least one of the other two of R^3 , R^5 and R^7 is not hydrogen; or
- (k) $-\text{W}^4\text{N}(\text{R}^{32})-\text{W}^5\text{NR}^{30}\text{R}^{31}$;
- R^1 and R^2 are selected from (i) or (ii) as follows:
- (i) R^1 is halide or is higher alkyl;
 R^2 is selected from:
- (a) hydrogen;
- (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, or aralkoxy, any of which may be substituted with W^1 , W^2 and W^3 ;
- (c) hydroxyl;
- (d) cyano;
- (e) nitro;
- (f) $-\text{C}(\text{O})\text{H}$ or $-\text{C}(\text{O})\text{R}^{27}$;
- (g) $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^{27}$;
- (h) $-\text{SH}$, $-\text{S}(\text{O})_n\text{R}^{27}$, $-\text{S}(\text{O})_m-\text{OH}$, $-\text{S}(\text{O})_m\text{OR}^{27}$, $-\text{O}-\text{S}(\text{O})_m-\text{R}^{27}$, $-\text{O}-\text{S}(\text{O})_m\text{OH}$, or $-\text{O}-\text{S}(\text{O})_m-\text{OR}^{27}$;

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- (i) $-W^4-NR^{28}R^{29}$; or
- (j) $-W^4N(R^{32})-W^5-NR^{30}R^{31}$; or
- (ii) R^1 and R^2 are each independently selected from:
- (a) hydrogen;
- 5 (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, or aralkoxy, any of which may be substituted with W^1 , W^2 and W^3 ;
- (c) hydroxyl;
- (d) cyano;
- 10 (e) nitro;
- (f) $-C(O)H$ or $-C(O)R^{27}$;
- (g) $-CO_2H$ or $-CO_2R^{27}$;
- (h) $-SH$, $-S(O)_nR^{27}$, $-S(O)_m-OH$, $-S(O)_mOR^{27}$, $-O-S(O)_m-R^{27}$, $-O-S(O)_mOH$, or $-O-S(O)_m-OR^{27}$;
- 15 (i) $-W^4-NR^{28}R^{29}$;
- (j) $-W^4N(R^{32})-W^5-NR^{30}R^{31}$; or
- (k) halo;
- R^{27} is alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;
- 20 R^{28} is
- (a) hydrogen;
- (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;
- 25 (c) cyano;
- (d) hydroxyl;
- (e) $-C(O)H$ or $-C(O)R^{27}$;
- (f) $-CO_2R^{27}$;
- (g) $-SH$, $-S(O)_nR^{27}$, $-S(O)_m-OH$, $-S(O)_m-OR^{27}$, $-O-S(O)_m-R^{27}$, $-O-S(O)_mOH$, or $-O-S(O)_m-OR^{27}$, except when W^4 is $-S(O)_n$;
- 30 R^{29} is
- (a) hydrogen;
- (b) $-C(O)H$ or $-C(O)R^{27}$, except when W^4 is $-C(O)-$ and R^{28} is $-C(O)H$, $-C(O)R^{27}$, or $-CO_2R^{27}$;

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- (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ; or

R^{28} and R^{29} together are alkylene or alkenylene (either of which may be substituted with W^1 , W^2 and W^3), completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached;

R^{30} is

- (a) hydrogen;
- (b) hydroxyl;
- (c) $-C(O)H$ or $-C(O)R^{27}$;
- (d) $-CO_2R^{27}$;
- (e) $-SH$, $-S(O)_nR^{27}$, $-S(O)_m-OH$, $-S(O)_m-OR^{27}$, $-O-S(O)_m-R^{27}$, $-O-S(O)_mOH$, or $-O-S(O)_m-OR^{27}$;
- (f) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

R^{31} is

- (a) hydrogen;
- (b) $-C(O)H$ or $-C(O)R^{27}$, except when W^5 is $-C(O)-$ and R^{30} is $-C(O)H$, $-C(O)R^{27}$, or $-CO_2R^{27}$; or
- (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

R^{32} is

- (a) hydrogen;
- (b) hydroxyl
- (c) $-C(O)H$, $-C(O)R^{27}$ or CO_2R^{27} ; or
- (d) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

or any two of R^{30} , R^{31} and R^{32} together are alkylene or alkenylene (either of which may be substituted with W^1 , W^2 and W^3), completing a 3- to 8-membered

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saturated, unsaturated or aromatic ring together with the atoms to which they are attached;

W^1 , W^2 and W^3 are each independently

- (a) hydrogen;
- 5 (b) halo;
- (c) hydroxy;
- (d) alkyl;
- (e) alkenyl;
- (f) aralkyl;
- 10 (g) alkoxy;
- (h) aryloxy;
- (i) aralkoxy;
- (j) $-SH$, $-S(O)_nW^6$, $-S(O)_m-OH$, $-S(O)_m-OW^6$, $-O-S(O)_m-W^6$,
 $-O-S(O)_mOH$, or $-O-S(O)_m-OW^6$;
- 15 (k) oxo;
- (l) nitro;
- (m) cyano;
- (n) $-C(O)H$ or $-C(O)W^6$;
- (o) $-CO_2H$ or $-CO_2W^6$;
- 20 (p) $-W^4-NW^7W^8$;
- (q) $W^4-N(W^{11})-W^5-W^6$; or
- (r) $-W^4-N(W^{11})-W^5-NW^7W^8$;

W^4 and W^5 are each independently

- (a) a single bond;
- 25 (b) $-W^9-S(O)_n-W^{10}-$;
- (c) $-W^9-C(O)-W^{10}-$;
- (d) $-W^9-C(S)-W^{10}-$;
- (e) $-W^9-O-W^{10}-$;
- (f) $-W^9-S-W^{10}-$; or
- 30 (g) $-W^9-O-C(O)-W^{10}-$;

W^6 , W^7 and W^8 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, or W^7 and W^8 together are alkylene or alkenylene, completing a 3- to 8-membered saturated,

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unsaturated or aromatic ring together with the nitrogen atom to which they are attached;

W^9 and W^{10} are each independently a single bond, alkylene, alkenylene, or alkynylene;

5 W^{11} is

- (a) hydrogen;
- (b) hydroxyl;
- (c) $-C(O)H$, $-C(O)W^8$ or $-CO_2W^8$;
- (d) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl;

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or any two of W^7 and W^8 and W^{11} together are alkylene or alkenylene, completing a 3- to 8-membered saturated, unsaturated, or aromatic ring together with the atoms to which they are attached;

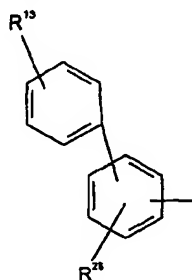
m is 1 or 2; and

15

n is 0, 1, or 2.

11. The method of any one of claims 6, 7, 9 or 10 in which Ar^2 is unsubstituted or substituted biphenyl group of formula (XIV):

20



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(XIV)

in which each ring has one or more substituents each selected independently from R^{26} and R^{13} where:

30

(i) R^{26} and R^{13} are independently selected from H, OH, OHNH, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, dialkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, carbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms, and are either straight or

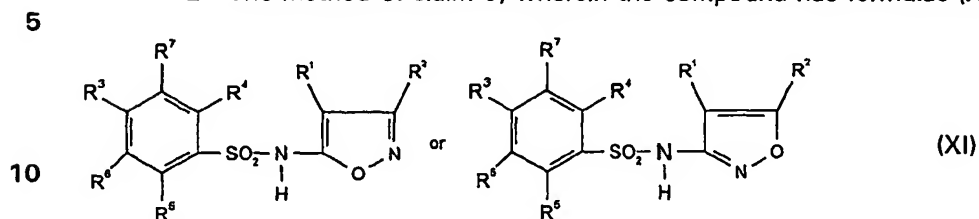
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branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons; or

(ii) R^{26} and R^{13} together are $-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, O, S, NR^{11} .

12. The method of claim 6, wherein the compound has formulae (XI):



15 which is substituted with R^4 , R^5 and R^6 which are selected independently, with the proviso that at least one of R^4 , R^5 and R^6 is not hydrogen:

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- (a) hydrogen;
 - (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;
 - (c) halo;
 - (d) hydroxyl;
 - (e) cyano;
 - (f) nitro;
 - (g) $-\text{C}(\text{O})\text{H}$ or $-\text{C}(\text{O})\text{R}^{27}$;
 - (h) $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^{27}$;
 - (i) $-\text{SH}$, $-\text{S}(\text{O})_n\text{R}^{27}$, $-\text{S}(\text{O})_m\text{OH}$, $-\text{S}(\text{O})_m\text{OR}^{27}$, $-\text{O-S}(\text{O})_m\text{R}^{27}$, $-\text{O-S}(\text{O})_m\text{OH}$, or $-\text{O-S}(\text{O})_m\text{OR}^{27}$;
 - (j) $-\text{W}^4\text{-NR}^{28}\text{R}^{29}$, or
 - (k) $-\text{W}^4\text{-N}(\text{R}^{32})\text{-W}^5\text{-NR}^{30}\text{R}^{31}$;

R^1 and R^2 are selected from (i) or (ii) as follows:

(i) R^1 is halide or higher alkyl;

R^2 is

- (a) hydrogen;
- (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;
- (c) hydroxyl;
- (d) cyano;

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- (e) nitro;
- (f) $-\text{C}(\text{O})\text{H}$ or $-\text{C}(\text{O})\text{R}^{27}$;
- (g) $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^{27}$;
- (h) $-\text{SH}$, $-\text{S}(\text{O})_n\text{R}^{27}$, $-\text{S}(\text{O})_m-\text{OH}$, $-\text{S}(\text{O})_m-\text{OR}^{27}$, $-\text{O}-\text{S}(\text{O})_m-\text{R}^{27}$, $-\text{O}-\text{S}(\text{O})_m\text{OH}$, or $-\text{O}-\text{S}(\text{O})_m-\text{OR}^{27}$;
- (i) $-\text{W}^4-\text{NR}^{28}\text{R}^{27}$; or
- (j) $-\text{W}^4-\text{N}(\text{R}^{32})-\text{W}^6-\text{NR}^{30}\text{R}^{31}$; or
- (ii) R^1 and R^2 are each independently selected from
- (a) hydrogen;
- (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;
- (c) hydroxyl;
- (d) cyano;
- (e) nitro;
- (f) $-\text{C}(\text{O})\text{H}$ or $-\text{C}(\text{O})\text{R}^{27}$;
- (g) $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^{27}$;
- (h) $-\text{SH}$, $-\text{S}(\text{O})_n\text{R}^{27}$, $-\text{S}(\text{O})_m-\text{OH}$, $-\text{S}(\text{O})_m-\text{OR}^{27}$, $-\text{O}-\text{S}(\text{O})_m-\text{R}^{27}$, $-\text{O}-\text{S}(\text{O})_m\text{OH}$, or $-\text{O}-\text{S}(\text{O})_m-\text{OR}^{27}$;
- (i) $-\text{W}^4-\text{NR}^{28}\text{R}^{27}$;
- (j) $-\text{W}^4-\text{N}(\text{R}^{32})-\text{W}^6-\text{NR}^{30}\text{R}^{31}$; or
- (k) halo;
- R^{27} is alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ,
- R^{28} is
- (a) hydrogen;
- (b) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;
- (c) cyano;
- (d) hydroxyl;
- (e) $-\text{C}(\text{O})\text{H}$ or $-\text{C}(\text{O})\text{R}^{27}$;
- (f) $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^{27}$;

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- (g) $-\text{SH}$, $-\text{S(O)}_n\text{R}^{27}$, $-\text{S(O)}_m-\text{OH}$, $-\text{S(O)}_m-\text{OR}^{27}$, $-\text{O-S(O)}_m-\text{R}^{27}$, $-\text{O-S(O)}_m\text{OH}$, or $-\text{O-S(O)}_m-\text{OR}^{27}$, except when W^4 is $-\text{S(O)}_n-$;

 R^{29} is

- (a) hydrogen;
- 5 (b) $-\text{C(O)H}$ or $-\text{C(O)R}^{27}$, except when W^4 is $-\text{C(O)}-$ and R^{28} is $-\text{C(O)H}$, $-\text{C(O)R}^{27}$, $-\text{CO}_2\text{H}$, or $-\text{CO}_2\text{R}^{27}$;
- (c) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 , or

- 10 R^{28} and R^{29} together are alkylene or alkenylene (either of which may be substituted with W^1 , W^2 and W^3), completing 3- to 8-membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached;

 R^{30} is

- (a) hydrogen;
- 15 (b) hydroxyl;
- (c) $-\text{C(O)H}$ or $-\text{C(O)R}^{27}$;
- (d) $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^{27}$;
- (e) $-\text{SH}$, $-\text{S(O)}_n\text{R}^{27}$, $-\text{S(O)}_m-\text{OH}$, $-\text{S(O)}_m-\text{OR}^{27}$, $-\text{O-S(O)}_m-\text{R}^{27}$, $-\text{O-S(O)}_m\text{OH}$, or $-\text{O-S(O)}_m-\text{OR}^{27}$;
- 20 (f) alkyl, alkynyl, alkenyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

 R^{31} is

- (a) hydrogen;
- 25 (b) $-\text{C(O)H}$ or $-\text{C(O)R}^{27}$, except when W^6 is $-\text{C(O)}-$ and R^{30} is $-\text{C(O)H}$, $-\text{C(O)R}^{27}$, $-\text{CO}_2\text{H}$, or $-\text{CO}_2\text{R}^{27}$;
- (c) alkyl, alkenyl, alkenyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

30 R^{32} is

- (a) hydrogen;
- (b) hydroxyl, CO_2R^{27} or CO_2H , except when one of R^{30} and R^{31} is hydroxyl, CO_2R^{27} or CO_2H ;
- (c) $-\text{C(O)H}$ or $-\text{C(O)R}^{27}$; or

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- (d) alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

or any two of R^{30} , R^{31} and R^{32} together are alkylene or alkenylene (either of which may be substituted with W^1 , W^2 and W^3), completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the atoms to which they are attached;

W^1 , W^2 and W^3 are each independently

- (a) hydrogen;
- (b) halo;
- (c) hydroxy;
- (d) alkoxy;
- (e) $-SH$, $-S(O)_nW^6$, $-S(O)_m-OH$, $-S(O)_m-OW^6$, $-O-S(O)_m-W^6$, $-O-S(O)_mOH$, or $-O-S(O)_m-OW^6$;
- (f) oxo;
- (g) nitro;
- (h) cyano;
- (i) $-C(O)H$ or $-C(O)W^6$;
- (j) $-CO_2H$ or $-CO_2W^6$; or
- (k) $-NW^7W^8$, $-C(O)NW^7W^8$, or $-S(O)_nW^7W^8$;

W^4 and W^5 are each independently

- (a) a single bond;
- (b) $-S(O)_n-$;
- (c) $-C(O)-$;
- (d) $-C(S)-$; or
- (e) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, any of which may be substituted with W^1 , W^2 and W^3 ;

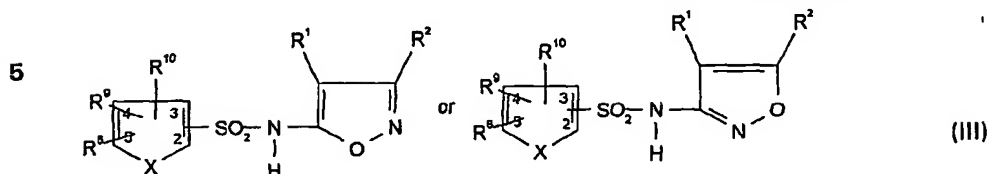
W^6 , W^7 and W^8 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, or aralkyl, or W^7 and W^8 together are alkylene or alkenylene, completing a 3- to 8-membered saturated, unsaturated or aromatic ring together with the nitrogen atom to which they are attached;

m is 1 or 2; and

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n is 0, 1, or 2.

13. The method of claim 6 or claim 8, wherein the compound has formulae III:



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in which R^1 , R^2 , are either (i), (ii) or (iii) as follows:

- (i) R^1 and R^2 are each independently selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, aminocarbonyl, haloalkyl, haloaryl, alkoxy, carbonyl, alkylcarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions are either straight or branched chains that contain from 1 up to about 10 carbon atoms, and the aryl portions contain from about 4 to about 14 carbons, except the R^2 is not halide, pseudohalide or higher alkyl; or,
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(ii) R^1 and R^2 together form $-(CH_2)_n$, where n is 3 to 6; or,

(iii) R^1 and R^2 together form 1,3-butadienyl; and

- X is O, S, N or NR^{11} , where R^{11} , which is hydrogen or contains up to about 30 carbon atoms, preferably 1 to 16 carbon atoms, and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{15}$ and $S(O)_nR^{15}$ in which n is 0-2; R^{15} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R^{11} and R^{15} are are unsubstituted or are substituted with one or more substituents each selected independently from Z, which is halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{16}$, CO_2R^{16} , SH, $S(O)_nR^{16}$ in which n is 0-2, NHOH, $NR^{12}R^{16}$, NO_2 , N_3 , OR^{16} , $R^{12}NCOR^{16}$ and $CONR^{12}R^{16}$; R^{16} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R^{12} , which is selected independently from R^{11} and Z, is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{17}$ and $S(O)_nR^{17}$ in which n is 0-2; and R^{17} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or
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cycloalkynyl; each of R^{11} , R^{12} , R^{15} and R^{16} may be further substituted with the any of the groups set forth for Z; and

R^8 , R^9 , R^{10} are each independently selected as follows from (i) or (ii):

- (i) R^8 , R^9 and R^{10} , which each contain hydrogen or up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, are each independently selected from hydrogen, halide pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{18}$, CO_2R^{18} , SH, $S(O)_nR^{18}$ in which n is 0-2, HNOH, $NR^{18}R^{19}$, NO_2 , N_3 , OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}$, in which R^{19} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{20}$, $S(O)_nR^{20}$ in which n is 0-2; and R^{18} and R^{20} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl or ureido; and any of the groups set forth for R^8 , R^9 and R^{10} are unsubstituted or substituted with any substituents set forth for Z, which is is halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{21}$, CO_2R^{21} , SH, $S(O)_nR^{21}$ in which n is 0-2, NHOH, $NR^{22}R^{21}$, NO_2 , N_3 , OR^{21} , $R^{22}NCOR^{21}$ and $CONR^{22}R^{21}$; R^{22} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_nR^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; or
- (ii) any two of R^8 , R^9 and R^{10} form an aryl, aromatic ring, heteroaromatic ring, alicyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to 7 members that is unsubstituted or substituted with one or more substituents in each each substituent is independently selected from Z; and the other of R^8 , R^9 and R^{10} is selected as in (i).

14. The method of claim 13, wherein X is S.
15. The method of any one of claims 1 to 5, wherein the endothelin receptor antagonist is a sulfonamide of formula I:



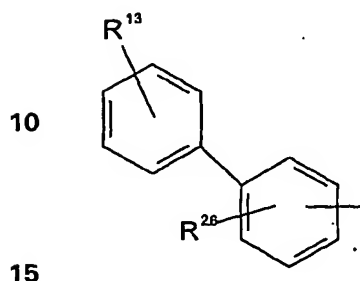
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or a veterinarily acceptable derivative thereof, wherein:

Ar¹ is a five or six membered aromatic or heteroaromatic ring, or is a bicyclic or tricyclic carbon or heterocyclic ring;

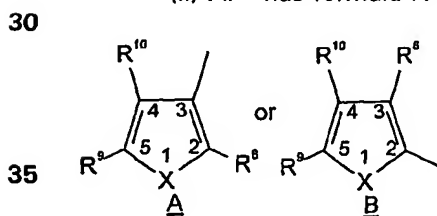
Ar² is either (i) or (ii):

5 (i) Ar² has formula (XIV):



wherein: Ar² is substituted with one or more than one substituent, each of which is selected independently from the selections set forth for R²⁶ and R¹³, in which R²⁶ and R¹³ are each independently selected from H, OH, OHNH, NH₂, NO₂, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, dialkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, carbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms, preferably from 1 to 6 atoms, and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons, preferably 4 to 10 carbons, with the proviso that if there is only one R¹³, it is not hydrogen; or

(ii) Ar² has formula IV:



in which X is S, O or NR¹¹ in which R¹¹ contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁵ and S(O)_nR¹⁶ in which n is 0-2; R¹⁵ is hydrogen, alkyl, alkenyl,

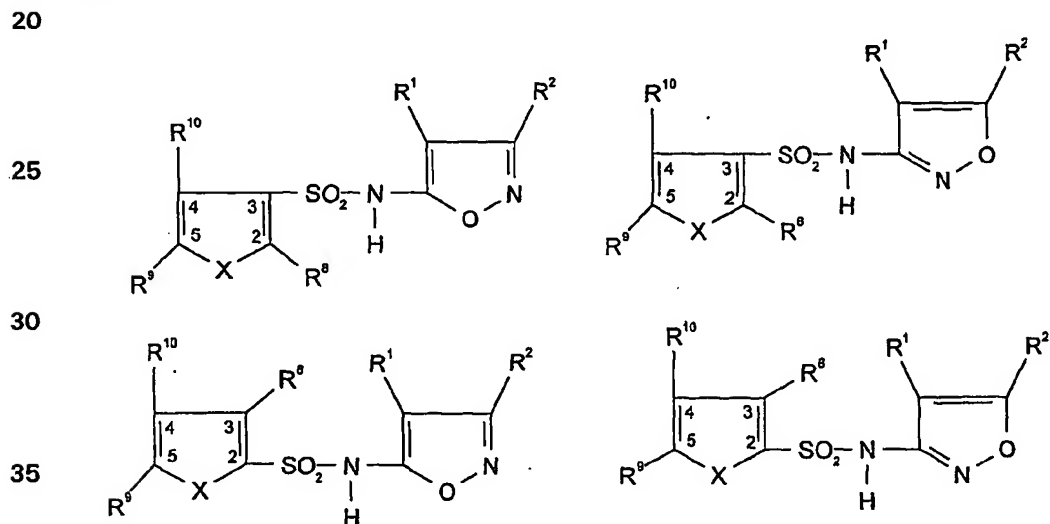
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- alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R^{11} and R^{15} are unsubstituted or are substituted with one or more substituents each selected independently from Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{16}$, CO_2R^{16} , SH, $S(O)_nR^{16}$ in which n is 0-2, NHOH, $NR^{12}R^{16}$, NO_2 , N_3 , OR^{16} , $R^{12}NCOR^{16}$ and $CONR^{12}R^{16}$; R^{16} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R^{12} , which is selected independently from R^{11} and Z, is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{17}$ and $S(O)_nR^{17}$ in which n is 0-2; and R^{17} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R^{11} , R^{12} , R^{15} and R^{16} may be further substituted with the any of the groups set forth for Z, and R^{11} is preferably hydrogen, aryl, such as phenyl or alkyl phenyl, loweralkyl; and R^8 , R^9 and R^{10} are each independently selected as follows from (i) or (ii):
- (i) R^8 , R^9 and R^{10} , which each contain hydrogen or up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, are each independently selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{18}$, acetoxymethyl, CO_2R^{18} , SH, $(CH_2)_rC(O)(CH_2)_sR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, $S(O)_mR^{18}$ in which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, HNOH, $NR^{18}R^{19}$, NO_2 , N_3 , OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}$, in which R^{19} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{20}$, $S(O)_nR^{20}$ in which n is 0-2; and R^{18} and R^{20} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; and any of the groups set forth for R^8 , R^9 and R^{10} are unsubstituted or substituted with any substituents set forth for Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{21}$, CO_2R^{21} , SH, $S(O)_nR^{21}$ in which n is 0-2, NHOH, $NR^{22}R^{21}$, NO_2 , N_3 , OR^{21} , $R^{22}NCOR^{21}$ and $CONR^{22}R^{21}$; R^{22} is selected from hydrogen, alkyl, alkenyl,

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- alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_nR^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl, with the proviso that if R^8 is $NR^{18}R^{19}$,
 5 OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}CO_2R^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$ or $(CH_2)_rR^{18}$ and R^{18} is an aryl group containing 5 or 6 members, then the aryl group has at least two substituents, and preferably one substituent at the 2-position relative to the linkage to the thienyl, furyl or pyrrolyl, or
 10 (ii) any two of R^8 , R^9 and R^{10} with the carbon to which each is attached form an aryl, aromatic ring, heteroaromatic ring, carbocyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to 7 members that is substituted with one or more substituents, each substituent is independently selected from Z ; the other of R^8 ,
 15 R^9 and R^{10} is selected as in (i); and the heteroatoms are NR^{11} , O, or S, with the proviso that Ar^2 is not 5-halo-3-loweralkylbenzo[b]thienyl, 5-halo-3-loweralkylbenzo[b]furyl, 5-halo-3-loweralkylbenzo[b]pyrrolyl.

16. The method of claim 15, wherein the compound has any of formulae XVII:



wherein: X is S, O or NR^{11} in which R^{11} contains up to about 30 carbon atoms,
 40 preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl,

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- cycloalkynyl, $C(O)R^{15}$ and $S(O)_nR^{15}$ in which n is 0-2; R^{15} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R^{11} and R^{15} are unsubstituted or are substituted with one or more substituents each selected independently from Z , which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH , CN , $C(O)R^{16}$, CO_2R^{16} , SH , $S(O)_nR^{16}$ in which n is 0-2, $NHOH$, $NR^{12}R^{16}$, NO_2 , N_3 , OR^{16} , $R^{12}NCOR^{16}$ and $CONR^{12}R^{16}$; R^{16} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R^{12} , which is selected independently from R^{11} and Z , is
- 5 selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{17}$ and $S(O)_nR^{17}$ in which n is 0-2; and R^{17} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R^{11} , R^{12} , R^{15} and R^{16} may be further substituted with the any of the groups set forth for Z , and R^{11} is preferably hydrogen,
- 10 aryl, such as phenyl or alkyl phenyl, loweralkyl; and
- R^8 , R^9 and R^{10} , which each contain hydrogen or up to about 50 carbon atoms, are each independently selected as described above, and more preferably from (i) or (ii) as follows:
- (i) R^9 and R^{10} are selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH , CN , $C(O)R^{18}$, $(OAC)CH=CHR^{18}$, CO_2R^{18} , SH , $(CH_2)_rC(O)(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $C=N(OH)(CH_2)_rR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, $S(O)_mR^{18}$ in
- 20 which m is 0-2, s , n and r are each independently 0 to 6, preferably 0-3, $HNOH$, $NR^{18}R^{19}$, NO_2 , N_3 , OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}$, in which R^{19} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{20}$, $S(O)_nR^{20}$ in which n is 0-2; and R^{18} and R^{20} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl,
- 25 heteroaryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl;
- 30

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R^8 is selected from $C(O)R^{18}$, $(OAC)CH=CHR^{18}$, CO_2R^{18} , $(CH_2)_rC(O)(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $C=N(OH)(CH_2)_rR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, in which m is 0-2, s , n and r are each independently 0 to 6, preferably 0-3, in which R^{18} is aryl, preferably phenyl, with the proviso that, if R^8 is $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, particularly if r is 0 and/or n is 0, and R^{18} is aryl, particularly phenyl, then R^{18} must have two or more substituents, with preferably at least one ortho substituent;

10 where any of the groups set forth for R^8 , R^9 and R^{10} are unsubstituted or substituted with any substituents set forth for Z , which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{21}$, CO_2R^{21} , SH, $S(O)_nR^{21}$ in which n is 0-2, $NHOH$, $NR^{22}R^{21}$, NO_2 , N_3 , OR^{21} , $R^{22}NCOR^{21}$ and $CONR^{22}R^{21}$; R^{22} is selected from
15 hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_nR^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; or

(ii) any two of R^8 , R^9 and R^{10} form an aryl, aromatic ring, heteroaromatic
20 ring, carbocyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to 7 members that is substituted with one or more substituents, each substituent being independently selected from Z ; the other of R^8 , R^9 and R^{10} is selected as from the groups set forth for R^9 and R^{10} in (i); and the heteroatoms are NR^{11} , O, or S, with the
25 proviso that Ar^2 is not 5-halo-3-loweralkylbenzo[b]thienyl, 5-halo-3-loweralkylbenzo[b]furyl, 5-halo-3-loweralkylbenzo[b]pyrrolyl; and

R^1 and R^2 are either (i), (ii) or (iii) as follows:

(i) R^1 and R^2 are each independently selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino,
30 alkylthio, alkyloxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up

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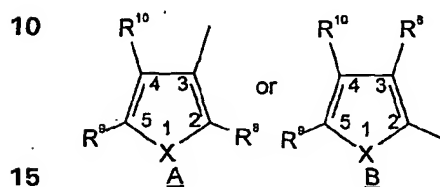
to about 14 carbon atoms and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons; or,

(ii) R^1 and R^2 together form $-(CH_2)_n$, where n is 3 to 6; or,

(iii) R^1 and R^2 together form 1,3-butadienyl.

5 17. The method of claim 15, wherein Ar^1 is an isoxazolyl, a thiazolyl, a pyrimidinyl, a pyridazinyl or a phenyl group.

18. The method of any one of claims 15 to 17, in which Ar^2 formula IVA or IVB:



wherein:

X is NR^{11} , O , or S ;

20 R^8 is selected from among $(CH_2)_rC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $C=N(OH)(CH_2)_rR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, with the proviso that if R^8 is

25 $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, or $(CH_2)_rR^{18}$, and R^{18} is phenyl, the phenyl group is substituted at least two positions;

and R^9 and R^{10} are independently selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH , CN , $C(O)R^{18}$, $(OAC)CH=CHR^{18}$, CO_2R^{18} , SH ,

30 $(CH_2)_rC(O)(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $C=N(OH)(CH_2)_rR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, $S(O)_mR^{18}$ in which m is 0-2, s , n and r are each independently 0 to 6, preferably 0-3, $HNOH$, $NR^{18}R^{18}$, NO_2 , N_3 , OR^{18} , $R^{18}NCOR^{18}$ and

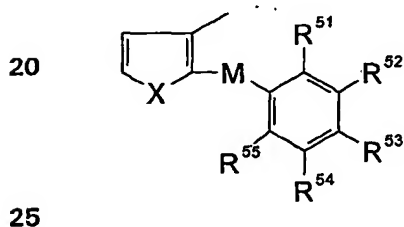
35 $CONR^{18}R^{18}$, in which R^{19} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{20}$, $S(O)_nR^{20}$ in which n is 0-2; and R^{18} and R^{20} are independently

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selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl.

19. The method of any one of claims 15 to 18, wherein Ar^2 is phenylamino-carbonylthienyl, phenylaminocarbonylfuryl, phenylaminocarbonylpyrrolyl, phenyl-acetylthiophene, phenylacetylfuran, phenylacetylpyrrole, acetoxystyrylthiophene, acetoxystyrylfuran or acetoxystyrylpyrrole, with the proviso that, when Ar^2 is a phenylaminocarbonylthienyl, phenylaminocarbonylfuryl, aminocarbonylpyrrolyl, the phenyl group is substituted with at least two substituents selected from Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH , CN , $C(O)R^{21}$, CO_2R^{21} , SH , $S(O)_nR^{21}$ in which n is 0-2, $NHOH$, $NR^{22}R^{21}$, NO_2 , N_3 , OR^{21} , $R^{22}NCOR^{21}$ and $CONR^{22}R^{21}$; R^{22} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_nR^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl.

20. The method of any one of claims 15 to 19, wherein Ar^2 has formula XIX:



wherein:

- M is $(CH_2)_mC(O)(CH_2)_r$, $(CH_2)_mC(O)NH(CH_2)_r$, $CH(OH)(CH_2)_r$, $(CH_2)_m(CH=CH)(CH_2)_r$, $(CH_2)_mC(O)(CH_2)_sNH(CH_2)_r$, $(CH_2)_m(CH=CH)(CH_2)_r$, $C=N(OH)(CH_2)_r$, $(CH_2)_mC(O)(CH=CH)_sNH(CH_2)_r$, $CH(CH_3)C(O)(CH_2)_r$, $CH(CH_3)C(O)(CH_2)_m(CH=CH)(CH_2)_r$, $(CH_2)_r$, $(CH_2)_rO$, $C(O)O$, in which m, s and r are each independently 0 to 6, preferably 0 to 3;
- 30

R^{51} , R^{52} , R^{53} , R^{54} and R^{55} are each independently selected from

(i) or (ii) as follows:

- 35 (i) R^{51} , R^{52} , R^{53} , R^{54} and R^{55} are each independently selected from among H , OH , NHR^{38} , $CONR^{38}R^{39}$, NO_2 , cyano, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, haloalkyl, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, alkylcarbonyl, alkenylthio, alkenylamino, alkenyloxy,

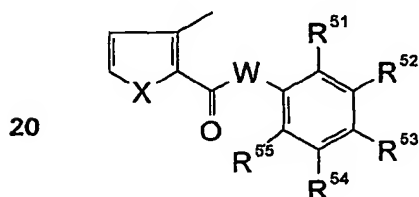
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alkenyl sulfinyl, alkenylsulfonyl, alkoxycarbonyl, arylaminocarbonyl, alkylaminocarbonyl, aminocarbonyl, (alkyl-aminocarbonyl)alkyl, carboxyl, carboxyalkyl, carboxyalkenyl, alkylsulfonylaminoalkyl, cyanoalkyl, acetyl, acetoxymethyl, hydroxymethyl, alkoxyalkoxy, hydroxymethyl, (acetoxymethyl)alkoxy, (hydroxymethyl)alkoxy and formyl; or

- 5 (ii) at least two of R^{51} , R^{52} , R^{53} , R^{54} and R^{55} , which substitute adjacent carbons on the ring, together form alkylenedioxy, alkylenethioxy or alkylenedithioxy, which is unsubstituted or substituted by replacing one or more hydrogens with halide, loweralkyl, loweralkoxy or halo loweralkyl, and the others of R^{51} , R^{52} , R^{53} , R^{54} and R^{55} are selected as in (i); and

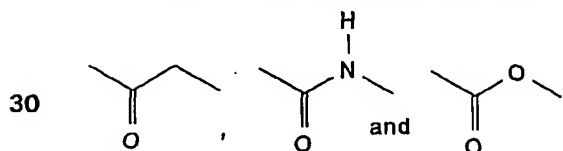
- 10 R^{38} and R^{39} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, haloalkyl alkylaryl, heterocycle, arylalkyl, arylalkoxy, alkoxy, aryloxy, cycloalkyl, cycloalkenyl and cycloalkynyl, and is preferably hydrogen, loweralkyl, loweralkoxy and lowerhaloalkyl, with the proviso that when M is $(CH_2)_mC(O)NH(CH_2)_n$, then at least two of R^{51} , R^{52} , R^{53} , R^{54} and R^{55} are not hydrogen.

- 15 21. The method of any one of claims 15 to 20, wherein Ar^2 has formula XX:



- 25 in which W is CH_2 or NH.

22. The method of claim 20, wherein M is selected from



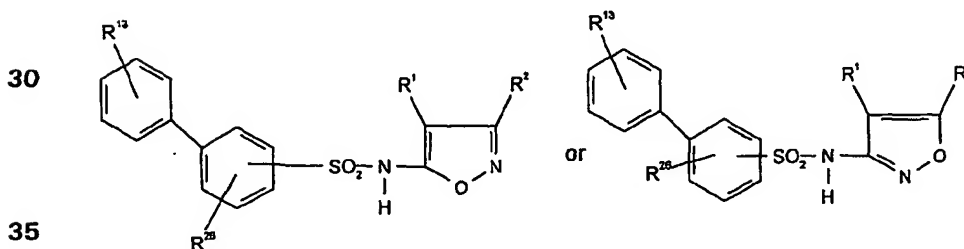
23. The method of any one of claims 15 to 18, wherein R^9 and R^{10} form a ring so that Ar^2 is benzo[b]thienyl, benzo[b]furyl, or indolyl, with the proviso that there is one or more substituent and they are other than 5-halo and 3-loweralkyl, and the other of R^8 , R^9 and R^{10} is selected from aryl, $(CH_2)_nR^{18}$, $C(O)R^{18}$, CO_2R^{18} , $NR^{18}R^{19}$, SH, $S(O)_nR^{18}$ in which n is 0-2, $HNOH$, NO_2 , N_3 , OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}$.

24. The method of claim 23, wherein the compound is selected from among

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- N-(4-bromo-3-methyl-5-isoxazolyl)-2-n-benzylbenzo[b]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-butylbenzo[b]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-*i*-propylbenzo[b]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-n-propylbenzo[b]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(4-ethylbenzyl)benzo[b]thiophene-3-sulfonamide;
- 5 N-(4-bromo-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)benzyl]benzo[b]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(3,4,5-trimethoxybenzyl)-benzo[b]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-ethyl-5-methylbenzo[b]thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)benzyl]benzo[b]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(3,4-dimethoxybenzyl)benzo[b]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-5-(benzo[b]thien-2-yl)thiophene-2-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(4-methoxybenzyl)benzo[b]thiophene-3-sulfonamide; N-(4-bromo-3-methyl-5-isoxazolyl)-2-(2-methoxybenzyl)-benzo[b]thiophene-3-sulfonamide; N-(3,4-
- 10 dimethyl-5-isoxazolyl)-2-(4-chlorobenzyl)benzo[b]thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-(4-dimethylaminobenzyl)benzo[b]thiophene-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-ethylbenzo[b]furan-3-sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-phenylbenzo[b]thiophene sulfonamide; N-(4-chloro-3-methyl-5-isoxazolyl)-6-methoxy-2-[3,4-(methylenedioxy)benzyl]benzo[b]thiophene-3-sul-
- 20 fonamide; and N-(4-chloro-5-methyl-3-isoxazolyl)-2-[3,4-(methylenedioxy)benzyl]-benzo[b]thiophene-3-sulfonamide.

25. The method of claim 15, wherein Ar² is thienyl.
26. The method of claim 15, wherein Ar² is furyl.
27. The method of claim 15, wherein Ar² is pyrrolyl.
- 25 28. The method of claim 15, wherein Ar² is biphenyl.
29. The method of claim 28, wherein the compound has formula XV:



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wherein Ar² is substituted with one or more than one substituent, each of which is selected independently from the selections set forth for R²⁶ and R¹³, and R²⁶ and R¹³ are each independently selected from H, loweralkyl, haloalkyl and halide.

30. The method of claim 28, wherein the compound is selected from among
 5 N-(4-bromo-3-methyl-5-isoxazolyl)-4'-methylphenyl-4-biphenylsulfonamide, (4-bromo-3-methyl-5-isoxazolyl)-4'-trifluorophenyl-4-biphenylsulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-4'-methoxyphenyl-4-biphenylsulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-3'-methoxyphenyl-4-biphenylsulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-2'-methoxyphenyl-4-biphenylsulfonamide and N-(4-bromo-3-methyl-5-isoxazolyl)-3',4'-
 10 methylenedioxyphenyl-4-biphenylsulfonamide.

31. The method of claim 28 or claim 29, wherein the compound is N-(4-bromo-3-methyl-5-isoxazolyl)-4'-methylphenyl-4-biphenylsulfonamide or N-(4-bromo-3-methyl-5-isoxazolyl)-4'-trifluorophenyl-4-biphenylsulfonamide.

32. The method of claim 15, wherein the compound is a (phenyl-
 15 acetyl)thiophenesulfonamide.

33. The method of claim 15, wherein the compound is selected from among
 N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)phenoxyacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)phenoxyacetyl]thiophene-3-sulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-2-[(3,4-methylenedioxy)phenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-[2-[3,4-(methylenedioxy)phenyl]acetyl]thiophene-3-sulfonamide oxime, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2-cyano-4,5-dimethoxyphenyl)aminocarbonyl]thiophene-3-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-2-(4-tolylacetylphenyl)-thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-hydroxy-4-
 25 methylphenyl]aminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2-cyano-4,5-(methylenedioxy)phenyl)aminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-2-(2,4-dimethylphenylacetyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,4-dimethylphenylacetyl)thiophene-3-sulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-2-(2,4-dimethylphenylacetyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)]phenylaminocarbonyl-3-thiophenesulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-(2-acetoxy-

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- ethyl)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-(2-hydroxyethyl)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,5-dimethylphenylacetyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methanesulfonylaminoethyl)-4,5-(methylenedioxy)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-cyanomethyl-4,5-(methylenedioxy)-6-cyanomethyl)-phenylaminocarbonyl-3-thiophenesulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-hydroxypropyl-4,5-(methylenedioxy)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-((dimethylamino)carbonylmethyl)-4,5-(methylenedioxy)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[β -acetoxystyryl-4,5-(methylenedioxy)styryl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(2,3,4-trimethoxy-6-cyano)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-3-(4-propylphenyl)thiophene-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)-phenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,4,6-trimethylphenylacetyl)thiophene-3-sulfonamide, N-(4-chloro-5-methyl-3-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)cinnamyl]thiophene-3-sulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-2-(2,4-dimethylphenethyl)thiophene-3-sulfonamide and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[(4-methoxycarbonyl-2,6-dimethyl)phenylaminocarbonyl]thiophene-3-sulfonamide or any corresponding N-(4-halo-3-methyl-5-isoxazolyl), N-(4-halo-5-methyl-3-isoxazolyl), N-(3,4-dimethyl-5-isoxazolyl), N-(4-halo-5-methyl-3-isoxazolyl), N-(4-halo-3-methyl-5-isoxazolyl), N-(4,5-dimethyl-3-isoxazolyl) derivative of any of these compounds.

34. The method of claim 15, wherein the compound is selected from among N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,3,4-trimethoxy-6-methylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,3,4-trimethoxy-6-acetylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,3,4-trimethoxy-6-methoxycarbonylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,3,4-trimethoxy-6-carboxylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,3,4-trimethoxy-6-methanesulfonylphenylaminocarbonyl)thio-

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- phene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2,3,4-trimethoxy-6-(cyanomethyl)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2,3,4-trimethoxy-6-(2-hydroxyethyl)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-acetylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-methoxycarbonylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-carboxylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-methanesulfonylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-cyanophenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-cyanomethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-(2-hydroxyethyl)phenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2,6-dimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-acetyl-2-methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methoxycarbonyl-2-methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-carboxyl-2-methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methoxy-2-methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methanesulfonyl-2-methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-cyano-2-methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-(cyanomethyl)-2-methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-(2-hydroxyethyl)-2-methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-cyano-6-methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methoxy-2-cyanophenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-acetyl-6-

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- methylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methoxy-2-acetylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxyl-2,4,6-trimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methanesulfonyl-2,4,6-trimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3-(2-hydroxyethyl)-2,4,6-trimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3-(carboxymethyl)-2,4,6-trimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(4-cyano-2,6-dimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(4-carboxyl-2,6-dimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[4-(2-hydroxyethyl)-2,6-dimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[4-(cyanomethyl)-2,6-dimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[4-(carboxymethyl)-2,6-dimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(4-methanesulfonyl-2,6-dimethylphenylaminocarbonyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,3,4-trimethoxy-6-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,3,4-trimethoxy-6-acetylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,3,4-trimethoxy-6-methoxycarbonylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,3,4-trimethoxy-6-carboxylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2,3,4-trimethoxy-6-methanesulfonylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2,3,4-trimethoxy-6-(cyanomethyl)phenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2,3,4-trimethoxy-6-(2-hydroxyethyl)phenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-acetylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-

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- 3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-methoxycarbonyl-phenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-carboxylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-methane-
- 5 sulfonylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-(cyano)phenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-(cyanomethylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-methoxy-6-(2-hydroxyethyl)phenylacetyl]thiophene-3-sulfonamide,
- 10 N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2,6-dimethylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-acetyl-2-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methoxycarbonyl-2-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-
- 15 (methylenedioxy)-6-carboxyl-2-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methoxy-2-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methanesulfonyl-2-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-cyano-2-
- 20 methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-(cyanomethyl)-2-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-(2-hydroxyethyl)-2-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-cyano-6-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-
- 25 methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methoxy-2-cyanophenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-2-acetyl-6-methylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)-6-methoxy-2-acetylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyano-2,4,6-trimethylphenylacetyl]thiophene-3-sulfonamide,
- 30 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxyl-2,4,6-trimethylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methanesulfonyl-2,4,6-trimethylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3-(cyanomethyl)-2,4,6-trimethylphenylacetyl]thiophene-3-sulfon-

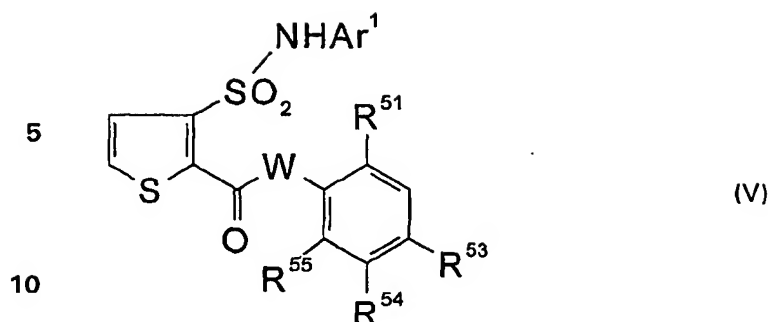
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amide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3-(2-hydroxyethyl)-2,4,6-trimethylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[3-(carboxylmethyl)-2,4,6-trimethylphenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(4-cyano-2,6-dimethylphenylacetyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(4-carboxyl-2,6-dimethylphenylacetyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(4-hydroxymethyl-2,6-dimethylphenylacetyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[4-(2-hydroxyethyl)-2,6-(dimethyl)phenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[4-cyanomethyl-2,6-(dimethyl)phenylacetyl]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[4-(carboxylmethyl)-2,6-dimethylphenylacetyl]thiophene-3-sulfonamide, and N-(4-chloro-3-methyl-5-isoxazolyl)-2-(4-methanesulfonyl-2,6-dimethylphenylacetyl)thiophene-3-sulfonamide or any corresponding N-(4-halo-3-methyl-5-isoxazolyl), N-(4-halo-5-methyl-3-isoxazolyl), N-(3,4-dimethyl-5-isoxazolyl), N-(4-halo-5-methyl-3-isoxazolyl), N-(4-halo-3-methyl-5-isoxazolyl), N-(4,5-dimethyl-3-isoxazolyl) derivative of any of these compounds.

35. The method of claim 15, wherein the compound is selected from among N-(4-chloro-3-methyl-5-isoxazolyl)-2-(N-(4-methyl-phenyl)aminocarbonyl)thiophene-3-sulfonamide, N-(4-bromo-3-methyl-5-isoxazolyl)-2-[3,4-(methylenedioxy)benzyl]benzo[b]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3,4-methylenedioxy)benzyl)benzo[b]thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[β -hydroxy(3,4-methylenedioxy)phenylethyl]thiophene-3-sulfonamide and N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3,4-methylenedioxybenzylcarbonyl)thiophene-3-sulfonamide or any corresponding N-(4-halo-3-methyl-5-isoxazolyl), N-(4-halo-5-methyl-3-isoxazolyl), N-(3,4-dimethyl-5-isoxazolyl), N-(4-halo-5-methyl-3-isoxazolyl), N-(4-halo-3-methyl-5-isoxazolyl), N-(4,5-dimethyl-3-isoxazolyl) derivative thereof.

36. The method of any one of claims 1 to 5, wherein the endothelin receptor antagonist is a sulfonamide of formula (V):

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or the corresponding 2-sulfonamides, or a veterinarily acceptable derivative thereof,
 15 wherein:

Ar¹ is a substituted or unsubstituted monocyclic or polycyclic aryl group with
 one or more substituents, selected from the group consisting of H, NH₂, halide,
 pseudohalide, alkyl, alkylcarbonyl, formyl, aryl, heteroaryl, alkoxyalkyl, alkylamino,
 alkylthio, arylcarbonyl, aryloxy, arylamino, arylthio, haloalkyl, haloaryl, and carbonyl, in
 20 which the aryl and alkyl portions are unsubstituted or substituted with any of the
 preceeding groups, and straight or branched chains of from about 1 up to about 10-12
 carbons;

R⁵¹, R⁵³, R⁵⁴ and R⁵⁵ are each independently selected from

(i) or (ii) as follows:

25 (i) R⁵¹, R⁵³, R⁵⁴ and R⁵⁵ are each independently selected from among H, OH,
 NHR³⁸, CONR³⁸R³⁹, NO₂, cyano, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl,
 arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, haloalkyl, alkylsulfinyl, alkylsulfonyl,
 alkoxy carbonyl, alkylcarbonyl, alkenylthio, alkenylamino, alkenyloxy, alkenyl sulfinyl,
 alkenylsulfonyl, alkoxy carbonyl, arylaminocarbonyl, alkylaminocarbonyl, aminocarbonyl,
 30 (alkyl-aminocarbonyl)alkyl, acetoxyl, hydroxyl, carboxyl, carboxyalkyl, carboxyalkenyl,
 alkylsulfonylaminoalkyl, cyanoalkyl, acetyl, acetoxylalkyl, hydroxylalkyl, alkoxyalkoxy,
 hydroxylalkyl, (acetoxyl)alkoxy, (hydroxyl)alkoxy, formyl, sulfonyl chlorides, amino acids,
 hexoses, O-glycosides, riboses, lower alkyl, CN, -(CH₂)_xC(O)(CH₂)_x, -(CH₂)_x, (CH₂)_x-
 lower alkyl, -(CH₂)_xC(O)NH₂, a D-, L- or racemic amino acid, a primary or secondary
 35 amide, O-glycoside, a hexose or ribose, -S(O)₂NH₂, hydroxy, alkoxy, alkoxy carbonyl,
 acetoxylalkyl, -(CH₂)_xCOOH; -(CH₂)_xCOOH-, CO₂-lower alkyl, CN, heteroaryl,
 -COC(O)(CH₂)_xCH₃, -(CH₂)_xN(CH₃)₂, a sulfonyl chloride, S(O)₂NHR⁵⁰, alkylaryl,
 alkylheteroaryl, C(O)NHR⁵⁰, -(CH₂)_xOH, -C(O)N(H)N(H)M, or;

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(ii) at least two of R^{51} , R^{53} , R^{54} and R^{55} , which substitute adjacent carbons on the ring, together form alkylenedioxy, alkylenethioxyoxy or alkylenedithioxy, which is unsubstituted or substituted by replacing one or more hydrogens with halide, loweralkyl, loweralkoxy or halo loweralkyl, and the others of R^{51} , R^{53} , R^{54} and R^{55} are selected as in

- 5 (i); R^{38} and R^{39} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, haloalkyl alkylaryl, heterocycle, arylalkyl, arylalkoxy, alkoxy, aryloxy, cycloalkyl, cycloalkenyl and cycloalkynyl.

37. The method of claim 36, wherein:

- 10 Ar^1 is benzo-2,1,3-thiadiazol-5-yl, benzo-2,1,3-oxadiazol-5-yl, 3-methoxy-2-pyrazinyl, 3,4-dimethyl-5-isoxazolyl, 4-chloro-3-methyl-5-isoxazolyl or 4-chloro-5-methyl-3-isoxazolyl;

W is $-NH-$, $=NCO_2R^{16}$, or is $-CH_2-$ when R^9 is hydroxyl;

R^{51} , R^{53} and R^{55} are methyl; and

- 15 R^{54} is selected from the group consisting of Z-substituted and unsubstituted alkyl, hydroxyl, substituted and unsubstituted alkoxy, $OC(O)R^{16}$, OCO_2R^{16} , $NR^{12}R^{16}$ and $S(O)_nR^{16}$ in which n is 0-2.

38. The method of claim 36 or claim 37, wherein R^{54} is selected from the group consisting of methoxy, methoxycarbonylmethoxy, 2-(2-methoxyethoxy)ethoxyacetoxy, 2-hydroxyethoxy, N,N-dimethylthiocarbonyloxy, N,N-dimethylthiocarbonyloxymethyl, 20 dimethylamino, pyrrolidinyl, acetoxy, hydroxy, cyanomethyl, acetoxymethyl, hydroxymethyl, carboxylmethyl, methanesulfonylamino, N,N-dimethylaminomethyl, SO_2NH_2 , and methoxycarbonylmethyl.

39. The method of any one of claims 36 to 38, wherein the sulfonamide or veterinarily acceptable derivative thereof is selected from the group consisting of:

- 25 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

- 30 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-pyrrolidinyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-dimethylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(N,N-dimethylthiocarbonyloxymethyl)-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

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- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(N,N-dimethylthiocarbonyloxy)-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(2-hydroxyethoxy)-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 5 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-(2-(2-methoxyethoxy)ethoxy)acetoxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonylmethoxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 10 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 15 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 20 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 25 N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 30 N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

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N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

5 N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-carboxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

10 N-(4-chloro-5-methyl-3-isoxazolyl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(3,4-dimethyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(3,4-dimethyl-5-isoxazolyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

15 N-(3,4-dimethyl-5-isoxazolyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(3,4-dimethyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

20 N-(3,4-dimethyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(3,4-dimethyl-5-isoxazolyl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(3,4-dimethyl-5-isoxazolyl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

25 N-(3,4-dimethyl-5-isoxazolyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(3,4-dimethyl-5-isoxazolyl)-2-(3-carboxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

30 N-(3,4-dimethyl-5-isoxazolyl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(3,4-dimethyl-5-isoxazolyl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

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- N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 5 N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 10 N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 15 N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-carboxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(benzo-2,1,3-thiadiazol-5-yl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 20 N-(3-methoxy-2-pyrazinyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(3-methoxy-2-pyrazinyl)-2-(3-methoxycarbonylmethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 25 N-(3-methoxy-2-pyrazinyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(3-methoxy-2-pyrazinyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(3-methoxy-2-pyrazinyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 30 N-(3-methoxy-2-pyrazinyl)-2-(3-dimethylaminomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(3-methoxy-2-pyrazinyl)-2-(3-methanesulfonylamino-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

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N-(3-methoxy-2-pyrazinyl)-2-(3-hydroxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

N-(3-methoxy-2-pyrazinyl)-2-(3-carboxy-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

5 N-(3-methoxy-2-pyrazinyl)-2-(3-cyano-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

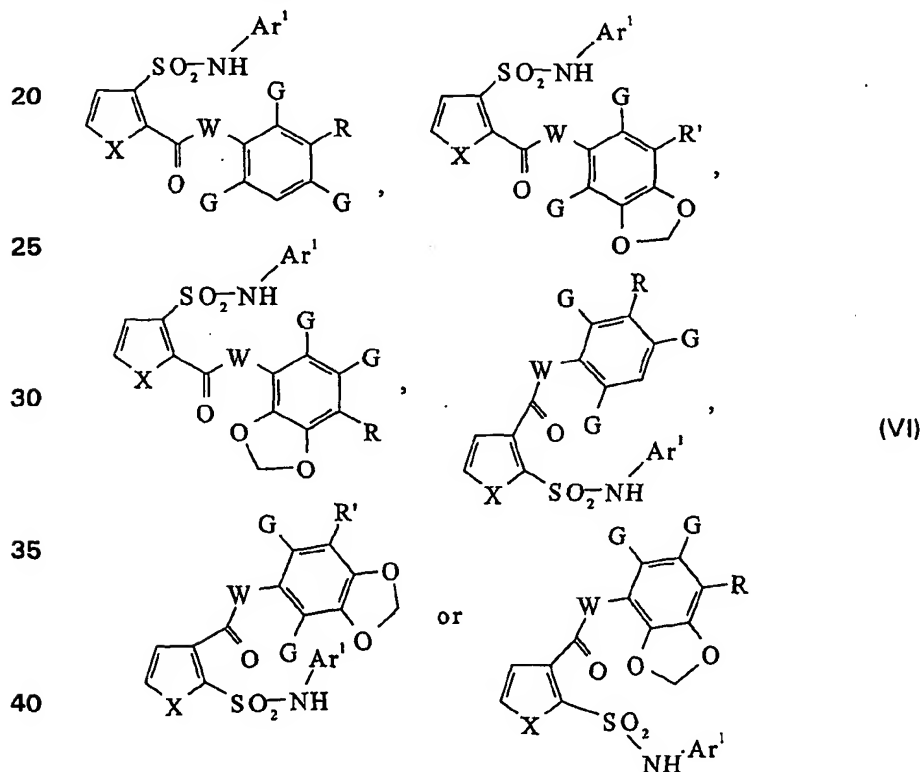
N-(3-methoxy-2-pyrazinyl)-2-(3-sulfamoyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;

10 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(1-methyl-1-phenyl-1-ethylaminocarbonyl)thiophene-3-sulfonamide;

N-(4-chloro-3-methyl-5-isoxazolyl)-2-((R)-1-phenyl-1-ethylaminocarbonyl)thiophene-3-sulfonamide;

N-(4-chloro-3-methyl-5-isoxazolyl)-2-((S)-1-phenyl-1-ethylaminocarbonyl)thiophene-3-sulfonamide; and veterinarily acceptable derivatives thereof.

15 40. The method of any one of claims 36 to 38, wherein the sulfonamide or veterinarily acceptable derivative thereof has formula VI:



wherein:

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X is S, O or NR¹¹;

each G and R is independently selected from lower alkyl, CN,

—(CH₂)_xC(O)(CH₂)_x, —(CH₂)_x, (CH₂)_xN-lower alkyl, —(CH₂)_xC(O)NH₂, a D-, L- or racemic amino acid, a primary or secondary amide, O-glycoside, a hexose or ribose, —S(O)₂NH₂,
 5 hydroxy, alkoxy, alkoxycarbonyl, acetoxyalkyl, —(CH₂)_xCOOH; —(CH₂)_xCOOH—, CO₂-lower alkyl, CN, heteroaryl, —COC(O)(CH₂)_xCH₃, —(CH₂)_xN(CH₃)₂, a sulfonyl chloride, S(O)₂NHR⁵⁰, alkylaryl, alkylheteroaryl, C(O)NHR⁵⁰, —(CH₂)_xOH, —C(O)N(H)N(H)M;

R⁵⁰ is hydrogen, lower alkyl, or lower alkoxy;

M is H or R⁵⁰;

10 R' is independently selected from hydrogen, G and R;

W is =C(halo)₂, =N(H), —(CH₂)_x—, =N(lower alkyl), —C(O)—, =C(lower alkyl)₂; and

each x is independently is 0-3.

41. The method of claim 40, wherein Ar¹ is isoxazolyl.

15 42. The method of claim 40 or claim 41, wherein:

W is =CH₂, =NH, =NCH₃, =NCH₂CH₃, =C(CH₃)₂ or CF₂; and

G is —CH₃, —CN, —COCH₃, —CH₂CH₃, —(CH₂)_xCO₂H.

43. The method of any one of claims 40 to 42, wherein the sulfonamide or
 20 veterinarianly acceptable derivative thereof is selected from the group consisting of:

N²-(3-cyanomethyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

methyl-2-(3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylphenyl)acetate;

25 2-(3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylphenyl)acetic acid;

N²-(3-acetyloxymethyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

N²-(3-hydroxymethyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

30 N²-(3-dimethylaminomethyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide trifluoroacetate;

N²-(3-(4,5-dihydro-1,3-oxazol-2-yl)-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

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3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylbenzoic acid;

N-[3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylbenzoyl]glutamic acid;

5 N-[3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylbenzoyl]aspartic acid;

N-[2-(3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylphenyl)acetyl]glutamic acid;

10 N-[2-(3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylphenyl)acetyl]aspartic acid;

N²-(3-cyano-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

2-(3-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-2,4,6-trimethylphenoxy)acetic acid;

15 N²-(3-alkylsulfonamido-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

N²-(3-arylsulfonamido-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

20 N²-(3-sulfamoyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

N²-(3-alkylsulfamoyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

N²-(3-arylsulfamoyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

25 N²-(3-(1H-1,2,3,4-tetraazol-5-ylmethyl)-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

N²-(3-(2-pyridylmethyl)-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

30 N²-(3-hydrazinocarbonyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

N²-(3-aminomethyl-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

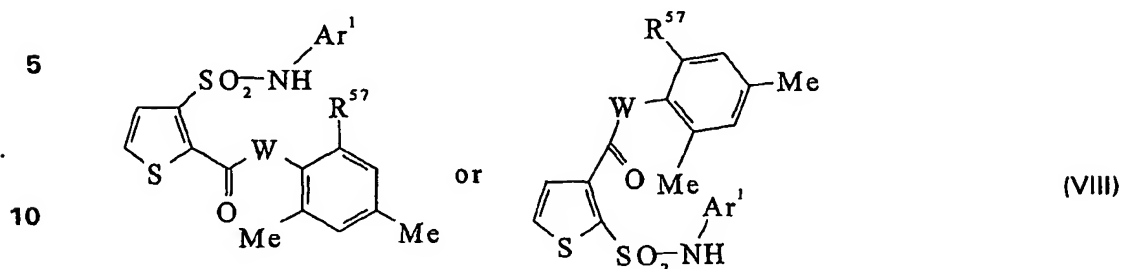
N²-(3-(α-D-mannopyranosyloxymethyl)-2,4,6-trimethylphenyl)-3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thiophenecarboxamide;

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- 5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-cyano-6-methylbenzo[d][1,3]dioxole;
- 5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-6-cyano-4-methylbenzo[d][1,3]dioxole;
- 5 2-(5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-methylbenzo[d][1,3]dioxole)-6-acetic acid;
- 5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-acetyl-6-methylbenzo[d][1,3]dioxole;
- 5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-6-acetyl-4-methylbenzo[d][1,3]dioxole;
- 10 5-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-7-cyano-4,6-dimethylbenzo[d][1,3]dioxole;
- 6-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-5,7-dimethylbenzo[d][1,3]dioxole-4-carboxylic acid;
- 15 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-5,6-dimethylbenzo[d][1,3]dioxole-4-carboxylic acid;
- 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-cyano-5,6-dimethylbenzo[d][1,3]dioxole;
- 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-acetyl-5,6-dimethylbenzo[d][1,3]dioxole;
- 20 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-carboxamido-5,6-dimethylbenzo[d][1,3]dioxole;
- 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-aminomethyl-5,6-dimethylbenzo[d][1,3]dioxole;
- 25 7-(3-(4-chloro-3-methyl-5-isoxazolylsulfamoyl)-2-thienylcarboxamido)-4-dimethylaminomethyl-5,6-dimethylbenzo[d][1,3]dioxole;
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-cyanomethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-carboxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- 30 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-acetoxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide;
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(3-hydroxymethyl-2,4,6-trimethylphenylaminocarbonyl)thiophene-3-sulfonamide; and veterinarily acceptable derivatives thereof.

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44. The method of claim 36 or claim 37, wherein the sulfonamide or
veterinarily acceptable derivative thereof is of formula (VIII):



wherein:

15 W is -NH-; and

R⁵⁷ is selected from the group consisting of aryl, heteroaryl, heterocycle, OH, CN, C(O)R¹⁶, CO₂R¹⁶, SH, S(O)_nR¹⁶ in which n is 0-2, a D, L or racemic amino acid, a ribose or hexose, an O-glycoside, a sulfonyl chloride, -(CH₂)_xOH, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶;

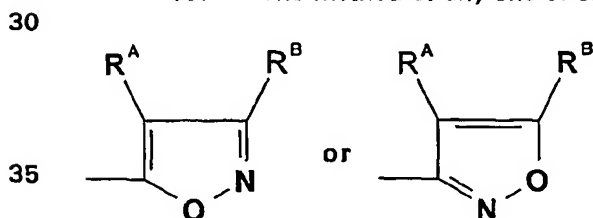
20 R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl;

R¹² is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2;

25 R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; and

each of R¹², R¹⁵ and R¹⁶ may be further substituted with the any of the groups set forth for Z.

45. The method of any one of claims 36 to 44, wherein Ar¹ has formula:



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in which R^A and R^B are either (i), (ii) or (iii) as follows:

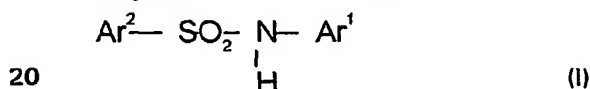
(i) R^A and R^B are each independently selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, alkyloxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons, except that R^2 is not halide or pseudohalide; or,

(ii) R^A and R^B together form $-(CH_2)_n$, where n is 3 to 6; or,

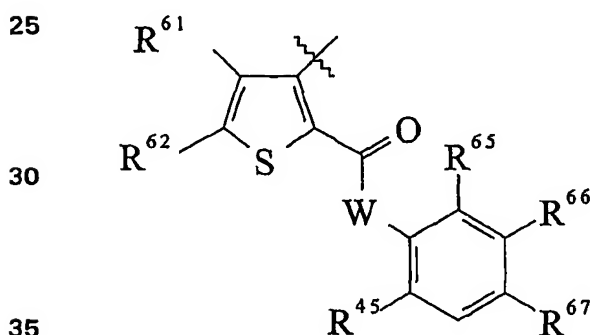
(iii) R^A and R^B together form 1,3-butadienyl.

46. The method of claim 36, wherein the compound is N^2 -(3-hydroxy-2,4,6-trimethyl)phenyl-3-(4-chloro-3-methyl-5-isoxazolyl)sulfamoyl-2-thiophenecarboxamide or a veterinarily acceptable derivative thereof.

47. The method of any one of claims 1 to 5, wherein the endothelin receptor antagonist is a sulfonamide of formula (I):



where Ar^1 is isoxazolyl and Ar^2 has the formula:



or a veterinarily acceptable derivative thereof, wherein:

R^{61} and R^{62} are independently selected from the group consisting of hydrogen, halo, cyano, cyanoalkyl, $C(O)R^{41}$, alkyl, alkenyl, cycloalkyl and aryl, or together form alkylene;

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W is O, NH or CH₂;

R⁶⁵, R⁶⁶ and R⁶⁷ are each independently selected as in (i) or (ii):

(i) R⁶⁶ is hydrogen, unsubstituted alkyl, hydroxy, unsubstituted alkoxy, C(O)R⁴¹, carbamoyloxy or alkoxycarbonyloxy, and

5 R⁶⁵ and R⁶⁷ are each independently selected from hydrogen, unsubstituted alkyl, hydroxy, C(O)R⁴¹, carbamoyloxy and alkoxycarbonyloxy; or

(ii) if at least one of R⁶¹ and R⁶² is not hydrogen, then any two may form alkylenedioxy, and the other is selected as in (i);

R⁴⁵ is selected from the group consisting of alkyl, C(O)R⁴¹, (CH₂)_xOH and
10 CH(OH)(CH₂)_xCH₃ in which x is 0-6, S(O)_nR⁴¹ in which n is 0-2 and C(=NR⁴³)R⁴¹;

R⁴¹ is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylsulfonylamino, arylsulfonylamino, alkylsulfonylalkylamino, alkylsulfonylarylamino, arylsulfonylalkylamino or arylsulfonylarylamino; and

15 R⁴³ is selected from hydroxy, alkoxy, alkyl and aryl, wherein

R⁴¹ and R⁴³ are unsubstituted or substituted with one or more substituents selected from Y, which is alkoxy, halide, pseudohalide, carboxyl, alkoxycarbonyl, aryloxycarbonyl or hydroxy.

48. The method of claim 47, wherein the sulfonamide is selected from the
20 group consisting of:

N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide,

N-(2-benzoyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide,

25 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-hydroxyethanimidoyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide,

3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-propionylphenyl)-2-thiophenecarboxamide,

30 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-isobutyryl-4,6-dimethylphenyl)-2-thiophenecarboxamide,

3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclohexylcarbonyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide,

3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclopropylcarbonyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide,

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- 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thienyl)carbonyl)amino)-2,4,6-trimethylphenyl carbamate,
- 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thienyl)carbonyl)amino)-2,4,6-trimethylphenyl methyl carbonate,
- 5 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-methoxy-2,4,6-trimethylphenyl)acetyl)-3-thiophenesulfonamide,
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-hydroxy-2,4,6-trimethylphenyl)acetyl)-3-thiophenesulfonamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-1-methylethyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide,
- 10 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-ethyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2,6-diacetyl)-4-methylphenyl)-2-thiophenecarboxamide,
- 15 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-methoxyacetyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide,
- 3-(2-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thienyl)carbonyl)amino)-3,5-dimethylphenyl)-3-oxopropanoic acid,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-glycolyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide,
- 20 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-methylsulfonyl)phenyl)-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((methylamino)sulfonyl)phenyl)-2-thiophenecarboxamide,
- 25 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((dimethylamino)sulfonyl)phenyl)-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-(((methylsulfonyl)amino)carbonyl)phenyl)-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-fluoroacetyl)-4,6-dimethylphenyl)-2-thiophenecarboxamide,
- 30 N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide,
- N-(2-benzoyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide,

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- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-hydroxyethanimidoyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-propionylphenyl)-5-methyl-2-thiophenecarboxamide,
- 5 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-isobutyryl-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclohexylcarbonyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclopropylcarbonyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide,
- 10 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(5-methylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl carbamate,
- 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(5-methylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl methyl carbonate,
- 15 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-methoxy-2,4,6-trimethylphenyl)acetyl)-5-methyl-3-thiophenesulfonamide,
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-hydroxy-2,4,6-trimethylphenyl)acetyl)-5-methyl-3-thiophenesulfonamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-1-methylethyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide,
- 20 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-ethyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2,6-diacetyl)-4-methylphenyl)-5-methyl-2-thiophenecarboxamide,
- 25 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-methoxyacetyl)-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide,
- 3-(2-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(5-methylthienyl))carbonyl)amino)-3,5-dimethylphenyl)-3-oxopropanoic acid,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-glycolyl-4,6-dimethylphenyl)-5-methyl-2-thiophenecarboxamide,
- 30 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-methylsulfonylphenyl)-5-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((methylamino)sulfonyl)phenyl)-5-methyl-2-thiophenecarboxamide,

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- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-
((dimethylamino)sulfonyl)phenyl)-5-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-
(((methylsulfonyl)amino)carbonyl)phenyl)-5-methyl-2-thiophenecarboxamide,
- 5 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-fluoroacetyl)-4,6-
dimethylphenyl)-5-methyl-2-thiophenecarboxamide,
- N-(6-acetyl-4-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-
isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide,
- N-(4-acetyl-6-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-
10 isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide,
- N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-
isoxazolyl)amino)sulfonyl)-4-methyl-2-thiophenecarboxamide,
- N-(2-benzoyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-
isoxazolyl)amino)sulfonyl)-4-methyl-2-thiophenecarboxamide,
- 15 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-hydroxyethanimidoyl)-
4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-
propionylphenyl)-4-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-isobutyryl-4,6-
20 dimethylphenyl)-4-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclohexylcarbonyl)-
4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclopropylcarbonyl)-
4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide,
- 25 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4-
methylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl carbamate,
- 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4-
methylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl methyl carbonate,
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-methoxy-2,4,6-
30 trimethylphenyl)acetyl)-4-methyl-3-thiophenesulfonamide,
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-hydroxy-2,4,6-trimethylphenyl)acetyl)-
4-methyl-3-thiophenesulfonamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-1-
methylethyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide,

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- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-ethyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2,6-diacetyl)-4-methylphenyl)-4-methyl-2-thiophenecarboxamide,
- 5 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-methoxyacetyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide,
- 3-(2-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4-methylthienyl))carbonyl)amino)-3,5-dimethylphenyl)-3-oxopropanoic acid,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-glycolyl-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide,
- 10 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-methylsulfonyl)phenyl)-4-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((methylamino)sulfonyl)phenyl)-4-methyl-2-thiophenecarboxamide,
- 15 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((dimethylamino)sulfonyl)phenyl)-4-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-(((methylsulfonyl)amino)carbonyl)phenyl)-4-methyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-fluoroacetyl)-4,6-dimethylphenyl)-4-methyl-2-thiophenecarboxamide,
- 20 N-(6-acetyl-4-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4-methyl-2-thiophenecarboxamide,
- N-(4-acetyl-6-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4-methyl-2-thiophenecarboxamide,
- 25 N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4,5-dimethyl-2-thiophenecarboxamide,
- N-(2-benzoyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-hydroxyethanimidoyl)-
- 30 4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-propionylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-isobutyryl-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,

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- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclohexylcarbonyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(cyclopropylcarbonyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 5 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4,5-dimethylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl carbamate,
- 3-(((3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4,5-dimethylthienyl))carbonyl)amino)-2,4,6-trimethylphenyl methyl carbonate,
- N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-methoxy-2,4,6-trimethylphenyl)acetyl)-4,5-dimethyl-3-thiophenesulfonamide,
- 10 N-(4-chloro-3-methyl-5-isoxazolyl)-2-(2-(3-hydroxy-2,4,6-trimethylphenyl)acetyl)-4,5-dimethyl-3-thiophenesulfonamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-1-methylethyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 15 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-hydroxy-ethyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2,6-diacetyl)-4-methylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-methoxyacetyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 20 3-(2-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-(4,5-dimethylthienyl))carbonyl)amino)-3,5-dimethylphenyl)-3-oxopropanoic acid,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-glycolyl-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 25 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-methylsulfonyl)phenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((methylamino)sulfonyl)phenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-((dimethylamino)sulfonyl)phenyl)-4,5-dimethyl-2-thiophenecarboxamide,
- 30 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2,4-dimethyl-6-(((methylsulfonyl)amino)carbonyl)phenyl)-4,5-dimethyl-2-thiophenecarboxamide, 3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-N-(2-(2-fluoroacetyl)-4,6-dimethylphenyl)-4,5-dimethyl-2-thiophenecarboxamide,

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N-(6-acetyl-4-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4,5-dimethyl-2-thiophenecarboxamide,

N-(4-acetyl-6-methyl-1,3-benzodioxol-5-yl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4,5-dimethyl-2-thiophenecarboxamide,

5 N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-cyclopropyl-2-thiophenecarboxamide,

5-acetyl-(N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide,

10 N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-cyano-2-thiophenecarboxamide,

N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-(cyanomethyl)-2-thiophenecarboxamide,

N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-fluoro-2-thiophenecarboxamide,

15 N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-chloro-2-thiophenecarboxamide, and

N-2-acetyl-4,6-dimethylphenyl)-5-chloro-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-4,5,6,7-tetrahydro-1-benzothiophene-2-carboxamide.

49. The method of claim 47, wherein the compound is selected from the group
20 consisting of N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide and N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide.

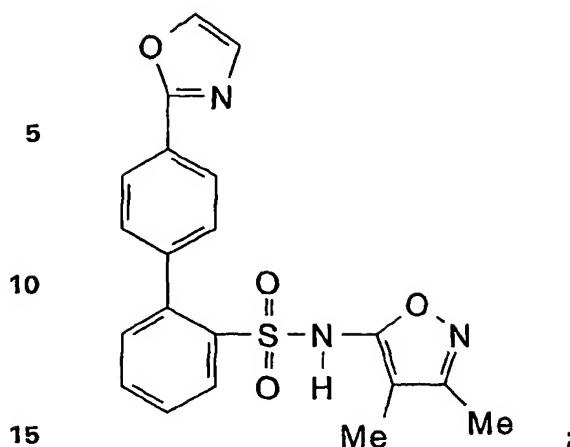
50. The method of any one of claims 1 to 5, wherein the endothelin receptor antagonist is the sulfonamide N-(4-chloro-3-methyl-5-isoxazolyl)-2-[[3,4-(methylenedioxy)-6-methylphenyl]acetyl]-thiophene-3-sulfonamide also designated 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide.

51. The method of any one of claims 1 to 5, wherein the endothelin receptor
30 antagonist is selected from the group consisting of:

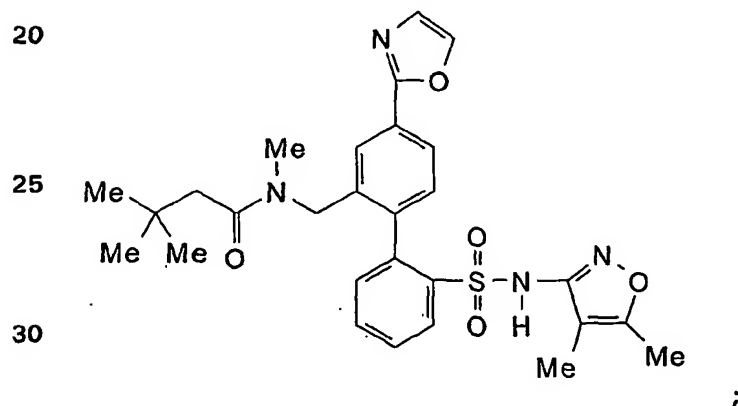
N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1, 1'-biphenyl]-2-sulfonamide, having the structure:

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N-[[2'-[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide, having the structure:

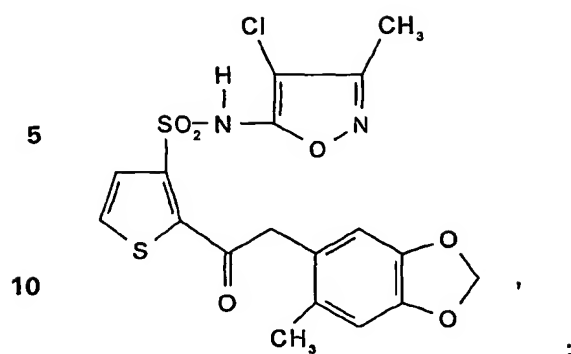


N-(4-chloro-3-methyl-5-isoxazolyl)-2-[[3,4-(methylenedioxy)-6-methylphenyl]-acetyl]-thiophene-3-sulfonamide also designated 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide, having the structure:

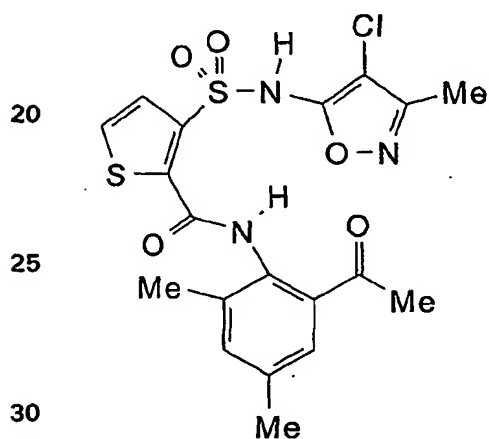
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15 N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide, having the structure:



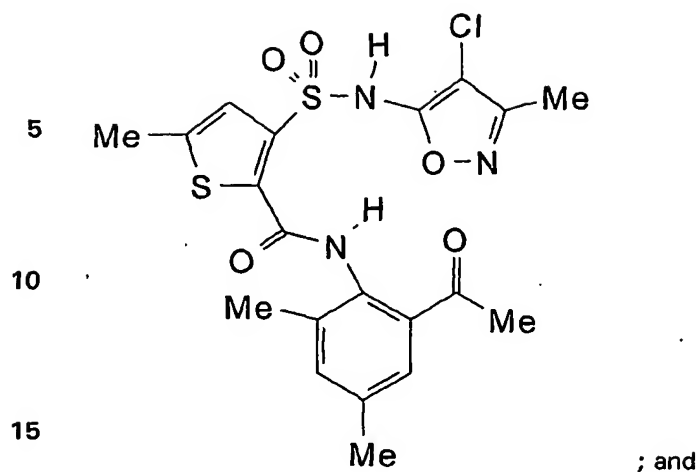
35 N-(2-acetyl-4,6-dimethylphenyl)-3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide, having the structure:

40

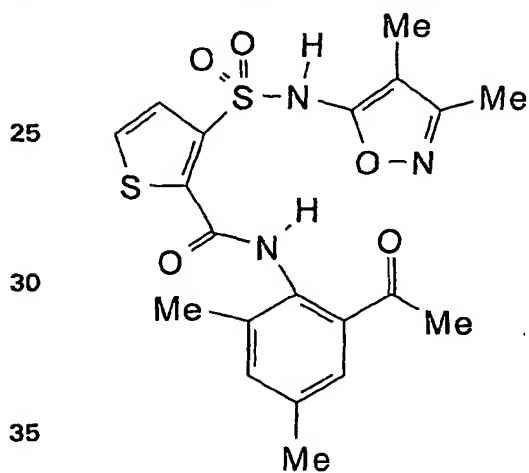
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20 N-(2-acetyl-4,6-dimethylphenyl)-3-(((3,4-dimethyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide, having the structure:



and veterinarily acceptable derivatives thereof.

40 52. The method of any one of claims 1 to 51, wherein the endothelin receptor antagonist is a sulfonamide that is a sodium salt.

53. A method of treating, preventing, or ameliorating one or more symptoms of climacterium (climacteric symptoms), comprising administering an effective amount of an endothelin receptor antagonist or a pharmaceutically acceptable derivative thereof.

45 54. The method of claim 53, further comprising administering an effective amount of a compound selected from an estrogen, a progestin and an androgen.

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55. The method of claim 53, further comprising administering an effective amount of (i) a nitric oxide synthase substrate; or (ii) a nitric oxide donor.

56. The method of claim 53, further comprising administering
 (i) an effective amount of a compound selected from an estrogen, a progestin
 5 and an androgen; and

(ii) an effective amount of (a) a nitric oxide synthase substrate; or (b) a nitric oxide donor.

57. The method of claim 53, wherein the climacteric symptoms are associated with menopause, osteoporosis, metabolic bone disorders, hot flashes,
 10 abnormal clotting patterns, urogenital discomfort and increased incidence of cardiovascular disease, and other disorders associated with the reduction in ovarian function in middle-aged women.

58. The method of claim 53, wherein the endothelin receptor antagonist is a sulfonamide or a pharmaceutically acceptable derivative thereof.

15 59. The method of any one of claims 53 to 58, wherein the endothelin receptor antagonist is a sulfonamide that has formula I:



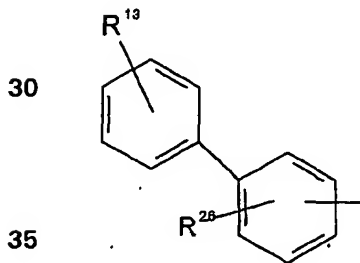
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or a pharmaceutically acceptable derivative thereof, wherein:

Ar¹ is a five or six membered aromatic or heteroaromatic ring, or is a bicyclic or tricyclic carbon or heterocyclic ring;

25 Ar² is either (i) or (ii):

(i) Ar² has formula (XIV):

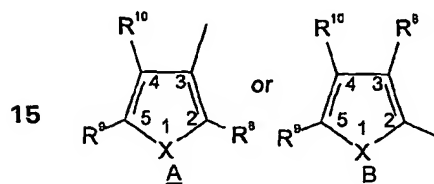


wherein: Ar² is substituted with one or more than one substituent, each of which is selected independently from the selections set forth for R²⁶ and R¹³, in which R²⁶ and
 40 R¹³ are each independently selected from H, OH, OHNH, NH₂, NO₂, halide, pseudohalide,

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alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, dialkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, carbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms, preferably from 1 to 6 atoms, and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons, preferably 4 to 10 carbons, with the proviso that if there is only one R^{13} , it is not hydrogen; or

(ii) Ar^2 has formula IV:



20 in which X is S, O or NR^{11} in which R^{11} contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{16}$ and $S(O)_nR^{16}$ in which n is 0-2; R^{16} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R^{11} and R^{15} are unsubstituted or are substituted with one or more substituents each selected independently from Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{16}$, CO_2R^{16} , SH, $S(O)_nR^{16}$ in which n is 0-2, NHOH, $NR^{12}R^{16}$, NO_2 , N_3 , OR^{16} , $R^{12}NCOR^{16}$ and $CONR^{12}R^{16}$; R^{16} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R^{12} , which is selected independently from R^{11} and Z, is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{17}$ and $S(O)_nR^{17}$ in which n is 0-2; and R^{17} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R^{11} , R^{12} , R^{15} and R^{16} may be further substituted with the any of the groups set forth for Z, and R^{11} is preferably hydrogen, aryl, such as phenyl or alkyl phenyl, loweralkyl; and R^8 , R^9 and R^{10} are each independently selected as follows from (i) or (ii):

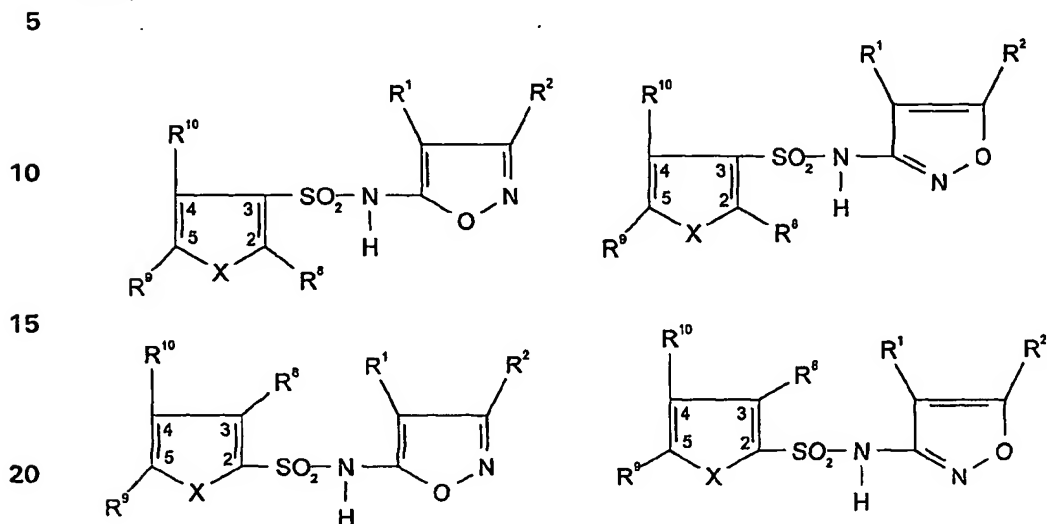
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- (i) R^8 , R^9 and R^{10} , which each contain hydrogen or up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, are each independently selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{18}$, acetoxymethyl, CO_2R^{18} , SH, $(CH_2)_rC(O)(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, $S(O)_mR^{18}$ in which m is 0-2, s , n and r are each independently 0 to 6, preferably 0-3, HNOH, $NR^{18}R^{19}$, NO_2 , N_3 , OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}$, in which R^{19} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{20}$, $S(O)_nR^{20}$ in which n is 0-2; and R^{18} and R^{20} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl;
- 15 and any of the groups set forth for R^8 , R^9 and R^{10} are unsubstituted or substituted with any substituents set forth for Z , which is hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{21}$, CO_2R^{21} , SH, $S(O)_nR^{21}$ in which n is 0-2, HNOH, $NR^{22}R^{21}$, NO_2 , N_3 , OR^{21} , $R^{22}NCOR^{21}$ and $CONR^{22}R^{21}$; R^{22} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_nR^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl, with the proviso that if R^8 is $NR^{18}R^{19}$, OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}$, CO_2R^{18} , $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$ or $(CH_2)_rR^{18}$ and R^{18} is an aryl group containing 5 or 6 members, then the aryl group has at least two substituents, and preferably one substituent at the 2-position relative to the linkage to the thienyl, furyl or pyrrolyl, or
- 25 (ii) any two of R^8 , R^9 and R^{10} with the carbon to which each is attached form an aryl, aromatic ring, heteroaromatic ring, carbocyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to 7 members that is substituted with one or more substituents, each substituent is independently selected from Z ; the other of R^8 , R^9 and R^{10} is selected as in (i); and the heteroatoms are NR^{11} , O, or S, with the proviso
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that Ar² is not 5-halo-3-loweralkylbenzo[b]thienyl, 5-halo-3-loweralkylbenzo[b]furyl, 5-halo-3-loweralkylbenzo[b]pyrrolyl.

60. The method of claim 59, wherein the compound has any of formulae XVII:



wherein: X is S, O or NR¹¹ in which R¹¹ contains up to about 30 carbon atoms,

preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁵ and S(O)_nR¹⁵ in which n is 0-2; R¹⁵ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R¹¹ and R¹⁵ are unsubstituted or are substituted with one or more

substituents each selected independently from Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁶, CO₂R¹⁶, SH, S(O)_nR¹⁶ in which n is 0-2, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶; R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹², which is selected independently from R¹¹ and Z, is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2; and R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R¹¹, R¹², R¹⁵ and R¹⁶ may be further

substituted with the any of the groups set forth for Z, and R¹¹ is preferably hydrogen, aryl, such as phenyl or alkyl phenyl, loweralkyl; and

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R^8 , R^9 and R^{10} , which each contain hydrogen or up to about 50 carbon atoms, are each independently selected as described above, and more preferably from (i) or (ii) as follows:

- (i) R^9 and R^{10} are selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{18}$, $(OAC)CH=CHR^{18}$, CO_2R^{18} , SH, $(CH_2)_rC(O)(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $C=N(OH)(CH_2)_rR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, $S(O)_mR^{18}$ in which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, $HNOH$, $NR^{18}R^{19}$, NO_2 , N_3 , OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}$, in which R^{19} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{20}$, $S(O)_nR^{20}$ in which n is 0-2; and R^{18} and R^{20} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl;
- R^8 is selected from $C(O)R^{18}$, $(OAC)CH=CHR^{18}$, CO_2R^{18} , $(CH_2)_rC(O)(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $C=N(OH)(CH_2)_rR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, in which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, in which R^{18} is aryl, preferably phenyl, with the proviso that, if R^8 is $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, particularly if r is 0 and/or n is 0, and R^{18} is aryl, particularly phenyl, then R^{18} must have two or more substituents, with preferably at least one ortho substituent;

- where any of the groups set forth for R^8 , R^9 and R^{10} are unsubstituted or substituted with any substituents set forth for Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{21}$, CO_2R^{21} , SH, $S(O)_nR^{21}$ in which n is 0-2, $NHOH$, $NR^{22}R^{21}$, NO_2 , N_3 , OR^{21} , $R^{22}NCOR^{21}$ and $CONR^{22}R^{21}$; R^{22} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_nR^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; or

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(ii) any two of R^8 , R^9 and R^{10} form an aryl, aromatic ring, heteroaromatic ring, carbocyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to 7 members that is substituted with one or more substituents, each substituent being
 5 independently selected from Z; the other of R^8 , R^9 and R^{10} is selected as from the groups set forth for R^8 and R^{10} in (i); and the heteroatoms are NR^{11} , O, or S, with the proviso that Ar^2 is not 5-halo-3-loweralkylbenzo[b]thienyl, 5-halo-3-loweralkylbenzo[b]furyl, 5-halo-3-loweralkylbenzo[b]pyrrolyl; and

R^1 and R^2 are either (i), (ii) or (iii) as follows:

10 (i) R^1 and R^2 are each independently selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, alkyloxy, haloalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or
 15 unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons; or,

(ii) R^1 and R^2 together form $-(CH_2)_n$, where n is 3 to 6; or,

(iii) R^1 and R^2 together form 1,3-butadienyl.

20 61. The method of claim 60, wherein Ar^2 is thienyl.

62. The method of claim 60, wherein the compound is a (phenyl-acetyl)thiophenesulfonamide.

63. The method of claim 60, wherein the compound is N-(4-chloro-3-methyl-5-isoxazolyl)-2- $\{[3,4$ -(methylenedioxy)-6-methylphenyl]acetyl}-thiophene-3-sulfonamide
 25 also designated 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide.

64. The method of claim 63, wherein the compound is a sodium salt.

65. The method of claim 60, wherein the compound is selected from the
 30 group consisting of:

N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1, 1'-biphenyl]-2-sulfonamide; N- $\{[2'$ - $\{[4,5$ -dimethyl-3-isoxazolyl]amino)sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]-methyl]-N,3,3-trimethylbutanamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2- $\{[3,4$ -(methylenedioxy)-6-methylphenyl]acetyl}-thiophene-3-sulfonamide also designated 4-

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chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide; N-(2-acetyl-4,6-dimethylphenyl)3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide; N-(2-acetyl-4,6-dimethylphenyl)3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide; and N-(2-acetyl-4,6-dimethylphenyl)-3-(((3,4-dimethyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide; and pharmaceutically acceptable derivatives thereof.

66. A method for control and management of preterm labor during pregnancy, comprising administering an effective amount of an endothelin receptor antagonist or a pharmaceutically acceptable derivative thereof.

67. The method of claim 66, further comprising administering an effective amount of a compound that augment an inducible nitric oxide synthase (iNOS) production.

68. The method of claim 66, wherein the endothelin receptor antagonist is a sulfonamide or a pharmaceutically acceptable derivative thereof.

69. The method of any one of claims 66 to 68, wherein the endothelin receptor antagonist is a sulfonamide of formula I:

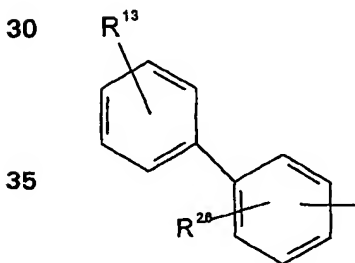


or a pharmaceutically acceptable derivative thereof, wherein:

Ar¹ is a five or six membered aromatic or heteroaromatic ring, or is a bicyclic or tricyclic carbon or heterocyclic ring;

Ar² is either (i) or (ii):

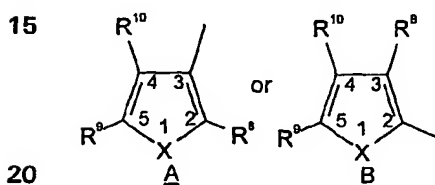
(i) Ar² has formula (XIV):



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wherein: Ar^2 is substituted with one or more than one substituent, each of which is selected independently from the selections set forth for R^{26} and R^{13} , in which R^{26} and R^{13} are each independently selected from H, OH, OHNH, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, dialkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, carbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms, preferably from 1 to 6 atoms, and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons, preferably 4 to 10 carbons, with the proviso that if there is only one R^{13} , it is not hydrogen; or

(ii) Ar^2 has formula IV:



in which X is S, O or NR^{11} in which R^{11} contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{16}$ and $S(O)_nR^{16}$ in which n is 0-2; R^{16} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R^{11} and R^{16} are unsubstituted or are substituted with one or more substituents each selected independently from Z, which is hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{16}$, CO_2R^{16} , SH, $S(O)_nR^{16}$ in which n is 0-2, $NHOH$, $NR^{12}R^{16}$, NO_2 , N_3 , OR^{16} , $R^{12}NCOR^{16}$ and $CONR^{12}R^{16}$; R^{16} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R^{12} , which is selected independently from R^{11} and Z, is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{17}$ and $S(O)_nR^{17}$ in which n is 0-2; and R^{17} is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R^{11} , R^{12} , R^{16} and R^{17} may be further

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substituted with the any of the groups set forth for Z, and R¹¹ is preferably hydrogen, aryl, such as phenyl or alkyl phenyl, loweralkyl; and R⁸, R⁹ and R¹⁰ are each independently selected as follows from (i) or (ii):

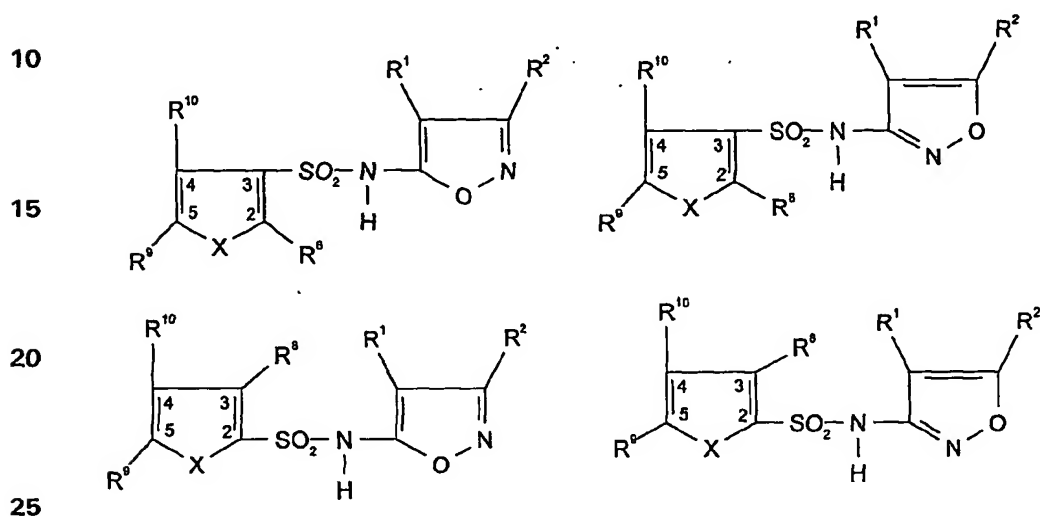
- (i) R⁸, R⁹ and R¹⁰, which each contain hydrogen or up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, are each independently selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁸, acetoxy-(CH=CH)-, CO₂R¹⁸, SH, (CH₂)_rC(O)(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_rC(O)(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sC(O)(CH₂)_nR¹⁸, (CH₂)_rNH(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sNH(CH₂)_nR¹⁸, (CH₂)_rC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rR¹⁸, S(O)_mR¹⁸ in which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, HNOH, NR¹⁸R¹⁹, NO₂, N₃, OR¹⁸, R¹⁹NCOR¹⁸ and CONR¹⁹R¹⁸, in which R¹⁹ is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²⁰, S(O)_nR²⁰ in which n is 0-2; and R¹⁸ and R²⁰ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; and any of the groups set forth for R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with any substituents set forth for Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R²¹, CO₂R²¹, SH, S(O)_nR²¹ in which n is 0-2, NHOH, NR²²R²¹, NO₂, N₃, OR²¹, R²²NCOR²¹ and CONR²²R²¹; R²² is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²³ and S(O)_nR²³ in which n is 0-2; and R²¹ and R²³ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl, with the proviso that if R⁸ is NR¹⁸R¹⁹, OR¹⁸, R¹⁹NCOR¹⁸ and CONR¹⁹R¹⁸ CO₂R¹⁸, (CH₂)_rNH(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sNH(CH₂)_nR¹⁸, (CH₂)_rC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸ or (CH₂)_rR¹⁸ and R¹⁸ is an aryl group containing 5 or 6 members, then the aryl group has at least two substituents, and preferably one substituent at the 2-position relative to the linkage to the thienyl, furyl or pyrrolyl, or

(ii) any two of R⁸, R⁹ and R¹⁰ with the carbon to which each is attached form an aryl, aromatic ring, heteroaromatic ring, carbocyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3

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to about 10 members, more preferably 5 to 7 members that is substituted with one or more substituents, each substituent is independently selected from Z; the other of R⁸, R⁹ and R¹⁰ is selected as in (i); and the heteroatoms are NR¹¹, O, or S, with the proviso that Ar² is not 5-halo-3-loweralkylbenzo[b]thienyl, 5-halo-3-loweralkylbenzo[b]furyl, 5-halo-3-loweralkylbenzo[b]pyrrolyl.

70. The method of claim 69, wherein the compound has any of formulae XVII:



wherein: X is S, O or NR¹¹ in which R¹¹ contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁵ and S(O)_nR¹⁵ in which n is 0-2; R¹⁵ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R¹¹ and R¹⁵ are unsubstituted or are substituted with one or more substituents each selected independently from Z, which is hydrogen, halide, pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁶, CO₂R¹⁶, SH, S(O)_nR¹⁶ in which n is 0-2, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶; R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹², which is selected independently from R¹¹ and Z, is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2; and R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy,

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cycloalkyl, cycloalkenyl or cycloalkynyl; each of R^{11} , R^{12} , R^{15} and R^{18} may be further substituted with the any of the groups set forth for Z, and R^{11} is preferably hydrogen, aryl, such as phenyl or alkyl phenyl, loweralkyl; and

- R^8 , R^9 and R^{10} , which each contain hydrogen or up to about 50 carbon atoms, are each independently selected as described above, and more preferably from (i) or (ii) as follows:

- (i) R^9 and R^{10} are selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{18}$, $(OAC)CH=CHR^{18}$, CO_2R^{18} , SH, $(CH_2)_rC(O)(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $C=N(OH)(CH_2)_rR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, $S(O)_mR^{18}$ in which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, HNOH, $NR^{18}R^{19}$, NO_2 , N_3 , OR^{18} , $R^{19}NCOR^{18}$ and $CONR^{19}R^{18}$, in which R^{19} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{20}$, $S(O)_nR^{20}$ in which n is 0-2; and R^{18} and R^{20} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl;
- R^8 is selected from $C(O)R^{18}$, $(OAC)CH=CHR^{18}$, CO_2R^{18} , $(CH_2)_rC(O)(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_rC(O)(CH=CH)_s(CH_2)_nR^{18}$, $(CH_2)_r(CH=CH)_sC(O)(CH_2)_nR^{18}$, $(CH_2)_rNH(CH=CH)_s(CH_2)_nR^{18}$, $C=N(OH)(CH_2)_rR^{18}$, $(CH_2)_r(CH=CH)_sNH(CH_2)_nR^{18}$, $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, in which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, in which R^{18} is aryl, preferably phenyl, with the proviso that, if R^8 is $(CH_2)_rC(O)NH(CH_2)_nR^{18}$, $C(O)(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rNH(CH_2)_nR^{18}$, $(CH_2)_rR^{18}$, particularly if r is 0 and/or n is 0, and R^{18} is aryl, particularly phenyl, then R^{18} must have two or more substituents, with preferably at least one ortho substituent;

- where any of the groups set forth for R^8 , R^9 and R^{10} are unsubstituted or substituted with any substituents set forth for Z, which is hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, $C(O)R^{21}$, CO_2R^{21} , SH, $S(O)_nR^{21}$ in which n is 0-2, HNOH, $NR^{22}R^{21}$, NO_2 , N_3 , OR^{21} , $R^{22}NCOR^{21}$ and $CONR^{22}R^{21}$; R^{22} is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy,

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cycloalkyl, cycloalkenyl, cycloalkynyl, $C(O)R^{23}$ and $S(O)_nR^{23}$ in which n is 0-2; and R^{21} and R^{23} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; or

- (ii) any two of R^8 , R^9 and R^{10} form an aryl, aromatic ring, heteroaromatic
 5 ring, carbocyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to 7 members that is substituted with one or more substituents, each substituent being independently selected from Z; the other of R^8 , R^9 and R^{10} is selected as from the groups set forth for R^9 and R^{10} in (i); and the heteroatoms are NR^{11} , O, or S, with the
 10 proviso that Ar^2 is not 5-halo-3-loweralkylbenzo[b]thienyl, 5-halo-3-loweralkylbenzo[b]furyl, 5-halo-3-loweralkylbenzo[b]pyrrolyl; and

R^1 and R^2 are either (i), (ii) or (iii) as follows:

- (i) R^1 and R^2 are each independently selected from H, NH_2 , NO_2 , halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino,
 15 alkylthio, alkyloxy, haloalkyl, alkylsulfinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsulfinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxy carbonyl, alkyl carbonyl, aminocarbonyl, aryl carbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms and are either straight or branched chains or cyclic, and the
 20 aryl portions contain from about 4 to about 16 carbons; or,

(ii) R^1 and R^2 together form $-(CH_2)_n$, where n is 3 to 6; or,

(iii) R^1 and R^2 together form 1,3-butadienyl.

71. The method of claim 70, wherein Ar^2 is thienyl.
 72. The method of claim 70, wherein the compound is a (phenyl-
 25 acetyl)thiophenesulfonamide.
 73. The method of claim 70, wherein the compound is N-(4-chloro-3-methyl-5-isoxazolyl)-2-([3,4-(methylenedioxy)-6-methylphenyl]acetyl)-thiophene-3-sulfonamide also designated 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-
 30 (methylenedioxy)phenylacetyl]thiophene-3-sulfonamide.

74. The method of claim 73, wherein the compound is a sodium salt.

75. The method of claim 70, wherein the compound is selected from the group consisting of N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1, 1'-biphenyl]-2-sulfonamide; N-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-4-(2-

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oxazolyl)[1,1'-biphenyl]-2-yl)methyl]-N,3,3-trimethylbutanamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-{{[3,4-(methylenedioxy)-6-methylphenyl]acetyl]-thiophene-3-sulfonamide also designated 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-

5 (methylenedioxy)phenylacetyl]thiophene-3-sulfonamide; N-(2-acetyl-4,6-dimethylphenyl)3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide; N-(2-acetyl-4,6-dimethylphenyl)3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide; and N-(2-acetyl-4,6-dimethylphenyl)-3-(((3,4-dimethyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide;

10 and pharmaceutically acceptable derivatives thereof.

76. Use of an endothelin receptor antagonist for treatment, prevention, or amelioration of one or more symptoms of laminitis.

77. The use of claim 76, wherein the laminitis is equine or bovine laminitis.

78. The use of claim 76 or claim 77, further comprising use of (i) a nitric

15 oxide synthase substrate; or (ii) a nitric oxide donor.

79. The use of claim 78, wherein:

the nitric oxide synthase substrate is L-arginine; and

the nitric oxide donor is sodium nitroprusside, nitroglycerin, glyceryl trinitrate, SIN-1, isosorbidmononitrate or isosorbiddinitrate.

80. The use of any one of claims 76 to 79, wherein the endothelin receptor antagonist is a sulfonamide or a veterinarily acceptable derivative thereof.

81. The use of any one of claims 76 to 80, wherein the endothelin receptor antagonist is a sulfonamide of formula I:



or a pharmaceutically acceptable derivative thereof, wherein:

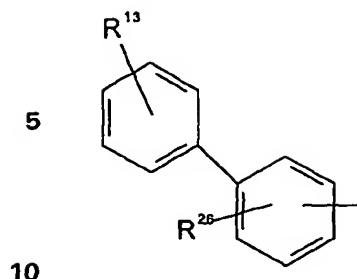
30 Ar^1 is a five or six membered aromatic or heteroaromatic ring, or is a bicyclic or tricyclic carbon or heterocyclic ring;

Ar^2 is either (i) or (ii):

(i) Ar^2 has formula (XIV):

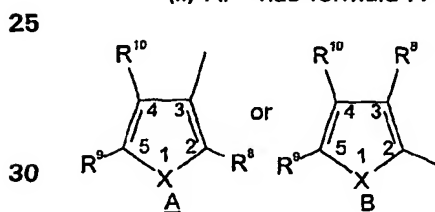
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wherein: Ar² is substituted with one or more than one substituent, each of which is selected independently from the selections set forth for R²⁶ and R¹³, in which R²⁶ and R¹³ are each independently selected from H, OH, OHNH, NH₂, NO₂, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterolaryl, alkoxy, alkylamino, dialkylamino, alkylthio, haloalkoxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, carbonyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms, preferably from 1 to 6 atoms, and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons, preferably 4 to 10 carbons, with the proviso that if there is only one R¹³, it is not hydrogen; or

(ii) Ar² has formula IV:



in which X is S, O or NR¹¹ in which R¹¹ contains up to about 30 carbon atoms, preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁵ and S(O)_nR¹⁵ in which n is 0-2; R¹⁵ is hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl; R¹¹ and R¹⁶ are unsubstituted or are substituted with one or more substituents each selected independently from Z, which is hydrogen, halide, pseudoalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy, cycloalkyl,

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- cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁶, CO₂R¹⁶, SH, S(O)_nR¹⁶ in which n is 0-2, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶; R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹², which is selected independently from R¹¹ and Z, is selected from
- 5 hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2; and R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R¹¹, R¹², R¹⁵ and R¹⁶ may be further substituted with the any of the groups set forth for Z, and R¹¹ is preferably hydrogen,
- 10 aryl, such as phenyl or alkyl phenyl, loweralkyl; and R⁸, R⁹ and R¹⁰ are each independently selected as follows from (i) or (ii):
- (i) R⁸, R⁹ and R¹⁰, which each contain hydrogen or up to about 50 carbon atoms, generally up to about 30, more generally 20 or fewer, are each independently selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl,
- 15 alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁸, acetoxy-(CH=CH)-, CO₂R¹⁸, SH, (CH₂)_rC(O)(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_rC(O)(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sC(O)(CH₂)_nR¹⁸, (CH₂)_rNH(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sNH(CH₂)_nR¹⁸, (CH₂)_rC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rR¹⁸, S(O)_mR¹⁸ in which m is 0-2, s, n
- 20 and r are each independently 0 to 6, preferably 0-3, HNOH, NR¹⁸R¹⁹, NO₂, N₃, OR¹⁸, R¹⁹NCOR¹⁸ and CONR¹⁹R¹⁸, in which R¹⁹ is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²⁰, S(O)_nR²⁰ in which n is 0-2; and R¹⁸ and R²⁰ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl,
- 25 heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; and any of the groups set forth for R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with any substituents set forth for Z, which is hydrogen, halide, pseudoalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R²¹, CO₂R²¹, SH, S(O)_nR²¹ in which n is 0-2, NHOH, NR²²R²¹,
- 30 NO₂, N₃, OR²¹, R²²NCOR²¹ and CONR²²R²¹; R²² is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²³ and S(O)_nR²³ in which n is 0-2; and R²¹ and R²³ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl, with the proviso that if R⁸ is NR¹⁸R¹⁹,

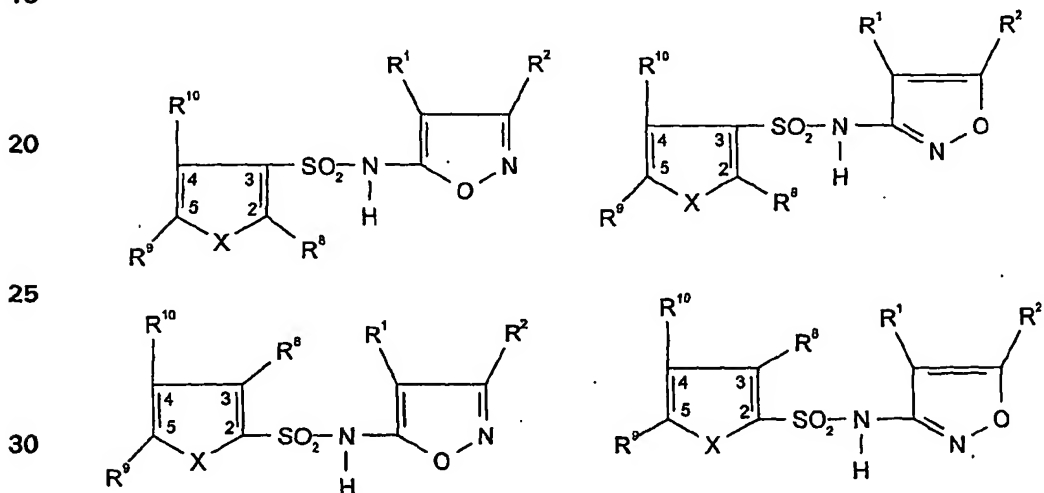
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OR¹⁸, R¹⁹NCOR¹⁸ and CONR¹⁹R¹⁸ CO₂R¹⁸, (CH₂)_iNH(CH=CH)_s(CH₂)_nR¹⁸,
 (CH₂)_i(CH=CH)_sNH(CH₂)_nR¹⁸, (CH₂)_iC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_iNH(CH₂)_nR¹⁸,
 (CH₂)_iNH(CH₂)_nR¹⁸ or (CH₂)_iR¹⁸ and R¹⁸ is an aryl group containing 5 or 6 members, then
 the aryl group has at least two substituents, and preferably one substituent at the 2-
 5 position relative to the linkage to the thienyl, furyl or pyrrolyl, or

(ii) any two of R⁸, R⁹ and R¹⁰ with the carbon to which each is attached
 form an aryl, aromatic ring, heteroaromatic ring, carbocyclic or heterocyclic ring, which
 is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3
 to about 10 members, more preferably 5 to 7 members that is substituted with one or
 10 more substituents, each substituent is independently selected from Z; the other of R⁸,
 R⁹ and R¹⁰ is selected as in (i); and the heteroatoms are NR¹¹, O, or S, with the proviso
 that Ar² is not 5-halo-3-loweralkylbenzo[b]thienyl, 5-halo-3-loweralkylbenzo[b]furyl, 5-
 halo-3-loweralkylbenzo[b]pyrrolyl.

81. The use of claim 80, wherein the compound has any of formulae XVII:

15



wherein: X is S, O or NR¹¹ in which R¹¹ contains up to about 30 carbon atoms,
 35 preferably 1 to 10, more preferably 1 to 6 and is selected from hydrogen, alkyl, alkenyl,
 alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl,
 cycloalkynyl, C(O)R¹⁵ and S(O)_nR¹⁵ in which n is 0-2; R¹⁵ is hydrogen, alkyl, alkenyl,
 alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl,
 cycloalkynyl; R¹¹ and R¹⁵ are unsubstituted or are substituted with one or more
 40 substituents each selected independently from Z, which is hydrogen, halide,
 pseudoalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, heterocycle, aralkyl, aralkoxy,

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cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁶, CO₂R¹⁶, SH, S(O)_nR¹⁶ in which n is 0-2, NHOH, NR¹²R¹⁶, NO₂, N₃, OR¹⁶, R¹²NCOR¹⁶ and CONR¹²R¹⁶; R¹⁶ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; R¹², which is selected independently from R¹¹ and Z, is
 5 selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R¹⁷ and S(O)_nR¹⁷ in which n is 0-2; and R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; each of R¹¹, R¹², R¹⁵ and R¹⁶ may be further substituted with the any of the groups set forth for Z, and R¹¹ is preferably hydrogen,
 10 aryl, such as phenyl or alkyl phenyl, loweralkyl; and

R⁸, R⁹ and R¹⁰, which each contain hydrogen or up to about 50 carbon atoms, are each independently selected as described above, and more preferably from (i) or (ii) as follows:

(i) R⁹ and R¹⁰ are selected from hydrogen, halide, pseudohalide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R¹⁸, (OAC)CH=CHR¹⁸, CO₂R¹⁸, SH, (CH₂)_rC(O)(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_rC(O)(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sC(O)(CH₂)_nR¹⁸, (CH₂)_rNH(CH=CH)_s(CH₂)_nR¹⁸, C=N(OH)(CH₂)_rR¹⁸, (CH₂)_r(CH=CH)_sNH(CH₂)_nR¹⁸, (CH₂)_rC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rR¹⁸, S(O)_mR¹⁸ in
 15 which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, HNOH, NR¹⁸R¹⁹, NO₂, N₃, OR¹⁸, R¹⁹NCOR¹⁸ and CONR¹⁹R¹⁸, in which R¹⁹ is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, alkoxy, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²⁰, S(O)_nR²⁰ in which n is 0-2; and R¹⁸ and R²⁰ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl,
 20 heteroaryl, alkylaryl, heterocycle, alkoxy, aryloxy, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl;

R⁸ is selected from C(O)R¹⁸, (OAC)CH=CHR¹⁸, CO₂R¹⁸, (CH₂)_rC(O)(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_rC(O)(CH=CH)_s(CH₂)_nR¹⁸, (CH₂)_r(CH=CH)_sC(O)(CH₂)_nR¹⁸, (CH₂)_rNH(CH=CH)_s(CH₂)_nR¹⁸, C=N(OH)(CH₂)_rR¹⁸, (CH₂)_r(CH=CH)_sNH(CH₂)_nR¹⁸, (CH₂)_rC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rR¹⁸, in which m is 0-2, s, n and r are each independently 0 to 6, preferably 0-3, in which R¹⁸ is aryl, preferably phenyl, with the proviso that, if R⁸ is (CH₂)_rC(O)NH(CH₂)_nR¹⁸, C(O)(CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rNH(CH₂)_nR¹⁸, (CH₂)_rR¹⁸, particularly if r is 0 and/or n is 0,
 30

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and R¹⁸ is aryl, particularly phenyl, then R¹⁸ must have two or more substituents, with preferably at least one ortho substituent;

where any of the groups set forth for R⁸, R⁹ and R¹⁰ are unsubstituted or substituted with any substituents set forth for Z, which is hydrogen, halide,

- 5 pseudoahlide, alkyl, alkoxy, alkenyl, alkynyl, aryl, aryloxy, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, OH, CN, C(O)R²¹, CO₂R²¹, SH, S(O)_nR²¹ in which n is 0-2, NHOH, NR²²R²¹, NO₂, N₃, OR²¹, R²²NCOR²¹ and CONR²²R²¹; R²² is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, alkoxy, aralkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, C(O)R²³ and S(O)_nR²³ in which n is 0-2; and R²¹
10 and R²³ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, alkylaryl, heterocycle, aralkyl, aralkoxy, cycloalkyl, cycloalkenyl or cycloalkynyl; or

- (ii) any two of R⁸, R⁹ and R¹⁰ form an aryl, aromatic ring, heteroaromatic ring, carbocyclic or heterocyclic ring, which is saturated or unsaturated, containing from about 3 to about 16 members, preferably 3 to about 10 members, more preferably 5 to
15 7 members that is substituted with one or more substituents, each substituent being independently selected from Z; the other of R⁸, R⁹ and R¹⁰ is selected as from the groups set forth for R⁹ and R¹⁰ in (i); and the heteroatoms are NR¹¹, O, or S, with the proviso that Ar² is not 5-halo-3-loweralkylbenzo[b]thienyl, 5-halo-3-loweralkylbenzo[b]furyl, 5-halo-3-loweralkylbenzo[b]pyrrolyl; and

- 20 R¹ and R² are either (i), (ii) or (iii) as follows:

- (i) R¹ and R² are each independently selected from H, NH₂, NO₂, halide, pseudohalide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, alkoxy, alkylamino, alkylthio, alkyloxy, haloalkyl, alkylsufinyl, alkylsulfonyl, aryloxy, arylamino, arylthio, arylsufinyl, arylsulfonyl, haloalkyl, haloaryl, alkoxycarbonyl, alkylcarbonyl,
25 aminocarbonyl, arylcarbonyl, formyl, substituted or unsubstituted amido, substituted or unsubstituted ureido, in which the alkyl, alkenyl and alkynyl portions contain from 1 up to about 14 carbon atoms and are either straight or branched chains or cyclic, and the aryl portions contain from about 4 to about 16 carbons; or,

- (ii) R¹ and R² together form -(CH₂)_n, where n is 3 to 6; or,
30 (iii) R¹ and R² together form 1,3-butadienyl.

82. The use of claim 81, wherein Ar² is thienyl.

83. The use of claim 81, wherein the compound is a (phenyl-acetyl)thiophenesulfonamide.

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84. The use of any one of claims 80 to 83, wherein the compound is N-(4-chloro-3-methyl-5-isoxazolyl)-2-[[3,4-(methylenedioxy)-6-methylphenyl]acetyl]-thiophene-3-sulfonamide also designated 4-chloro-3-methyl-5-{2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido}isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide.

85. The use of claim 84, wherein the compound is a sodium salt.

86. The use of claim 81, wherein the compound is selected from the group consisting of N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1, 1'-biphenyl]-2-sulfonamide; N-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-[[3,4-(methylenedioxy)-6-methylphenyl]acetyl]-thiophene-3-sulfonamide also designated 4-chloro-3-methyl-5-{2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido}isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide; N-(2-acetyl-4,6-dimethylphenyl)3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide; N-(2-acetyl-4,6-dimethylphenyl)3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide; and N-(2-acetyl-4,6-dimethylphenyl)-3-(((3,4-dimethyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide; and pharmaceutically acceptable derivatives thereof.

87. Use of an endothelin receptor antagonist for preparation of a medicament for treatment, prevention, or amelioration of one or more symptoms of laminitis.

88. The use of claim 87, wherein the laminitis is equine or bovine laminitis.

89. The use of claim 87 or claim 88, wherein the compound is N-(4-chloro-3-methyl-5-isoxazolyl)-2-[[3,4-(methylenedioxy)-6-methylphenyl]acetyl]-thiophene-3-sulfonamide also designated 4-chloro-3-methyl-5-{2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido}isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-(methylenedioxy)phenylacetyl]thiophene-3-sulfonamide.

90. The use of claim 89, wherein the compound is a sodium salt.

91. The use of claim 87 or claim 88, wherein the compound is selected from the group consisting of N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)[1, 1'-biphenyl]-2-sulfonamide; N-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-4-(2-

-356-

- oxazolyl)[1,1'-biphenyl]-2-yl)methyl]-N,3,3-trimethylbutanamide; N-(4-chloro-3-methyl-5-isoxazolyl)-2-([3,4-(methylenedioxy)-6-methylphenyl]acetyl)-thiophene-3-sulfonamide also designated 4-chloro-3-methyl-5-(2-(2-(6-methylbenzo[d][1,3]dioxol-5-yl)acetyl)-3-thienylsulfonamido)isoxazole and N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-methyl-4,5-
5. (methylenedioxy)phenylacetyl]thiophene-3-sulfonamide; N-(2-acetyl-4,6-dimethylphenyl)3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide; N-(2-acetyl-4,6-dimethylphenyl)3-(((4-chloro-3-methyl-5-isoxazolyl)amino)sulfonyl)-5-methyl-2-thiophenecarboxamide; and N-(2-acetyl-4,6-dimethylphenyl)-3-(((3,4-dimethyl-5-isoxazolyl)amino)sulfonyl)-2-thiophenecarboxamide;
- 10 and pharmaceutically acceptable derivatives thereof.

92. Use of an endothelin antagonist for the treatment of menopausal conditions or symptoms or for treatment of pregnancy-related disorders.

93. Use of an endothelin antagonist for the formulation of a medicament for the treatment of menopausal conditions or symptoms or for the treatment of
- 15 pregnancy-related disorders.

94. The use of claim 92 or claim 93, wherein the symptoms are one or more of osteoporosis, metabolic bone disorders, hot flashes, abnormal clotting patterns, urogenital discomfort and increased incidence of cardiovascular disease, and other disorders associated with the reduction in ovarian function in middle-aged women; pre-
- 20 eclampsia; and control and management of labor during pregnancy.

INTERNATIONAL SEARCH REPORT

International Application No

PCT, 00/35280

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/42 A61P9/00 A61P15/06 A61P15/12 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 281 207 A (UNIV SHEFFIELD) 1 March 1995 (1995-03-01) abstract claims 1-33 ---	1-94
X	US 5 981 579 A (HENDERSON IAN WILLIAM ET AL) 9 November 1999 (1999-11-09) abstract column 4, line 34 - line 37 claims 1-6 ---	1-94
X	WO 98 49162 A (KOGAN TIMOTHY ;BLOK NATALIE (US); KELLER KARIN (US); WU CHENGDE (U)) 5 November 1998 (1998-11-05) abstract page 8, line 22 -page 9, line 20 page 20, line 3 - line 17 claims 1-81 --- -/--	1-94

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

13 March 2001

Date of mailing of the international search report

12.06.01

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/ 00/35280

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 39000 A (TEXAS BIOTECHNOLOGY CORP) 23 October 1997 (1997-10-23) cited in the application abstract page 8, line 16 - line 26 page 19, line 7 - line 21 claims 1-30 ---	1-94
X	WO 96 31492 A (TEXAS BIOTECHNOLOGY CORP ;CHAN MING FAI (US); RAJU BORE GOWDA (US)) 10 October 1996 (1996-10-10) abstract page 20, line 23 -page 21, line 3 claims 1-84 ---	1-94
X	WO 95 06467 A (UNIV SHEFFIELD ;HENDERSON IAN WILLIAM (GB); HINCKLEY KAREN ANN (GB) 9 March 1995 (1995-03-09) abstract page 12, line 4 - line 22 examples 1-4 claims 20,30 ---	1-94
P,X	WO 00 01389 A (BRISTOL MYERS SQUIBB CO) 13 January 2000 (2000-01-13) abstract page 45, line 1 -page 47, line 23 page 142 -page 174 claims 1-59 -----	1-94

INTERNATIONAL SEARCH REPORT

Int'l application No.
PCT/US 00/35280**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-86 and 92-94 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 52, 76 - 91

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Present claims 1-92 relate to an extremely large number of possible compounds/products. In fact, the claims contain so many options and possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

For example, certain compounds falling within the scope of claim 40 do not fall within the scope of structure (V) given in claim 36. Moreover, the expression in claim 36 "or the corresponding 2-sulphonamides" is vague and indefinite in that it does not clearly define which 2-sulphonamides are intended. Thus, this could mean the thiophene 2-sulphonamide derivatives (having no other substituents); the 2-sulphonamide 5-CO-W-X derivatives; or the 2-sulphonamide 3-CO-W-X derivatives.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-52,76-91

The use of endothelin receptor antagonists for the treatment of one or more of the symptoms of laminitis.

2. Claims: 53-65,92-94

The use of endothelin receptor antagonists for the treatment of climacteric conditions.

3. Claims: 66-75

The use of endothelin receptor antagonists for the treatment of pre-term labour.

4. Claims: 92-94

The use of endothelin receptor antagonists for the treatment of pregnancy-related disorders.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/ 00/35280

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